Outcomes of childhood acute lymphoblastic leukemia treated with the modified St Jude Total Therapy XV Protocol: a single-center experience in Turkey

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April 05, 2024

Abstract

Background When developed countries are considered; in the treatment of childhood acute lymphoblastic leukemia (ALL), the survival rate has reached 90% in recent years. We aimed to examine the survival rate and the factors that may affect this rate, especially in our patients treated with the ST Jude Total Therapy XV protocol. Procedures Pediatric patients aged 1-18 years, who were treated at our hospital and completed their treatment between January 2011 and December 2018, and only pre-B and T-cell leukemias treated with the St Jude Total Therapy XV protocol were included in the study. Results The 5-year event-free survival (EFS) and overall survival (OS) were 78.3% and 80%. We observed that some factors that affect survival, such as gender, blastic type, risk group, and number of WBCs, did not affect survival in our study. Even though it is known that the female gender has better EFS, in our study, the survival of girls was found to be lower than boys. Tragically, we observed that the most common cause of death (20/23, 87%) was infection and infection-related causes. Conclusions The primary purpose of the St Jude Total XV treatment protocol is to monitor minimal residual disease (MRD) and to guide treatment according to MRD results. It is also the removal of radiotherapy from treatment protocols by adding additional intra-thecal treatments (ITT). However, unfortunately, if we cannot protect our patients from infection and other related factors, the factors that make a difference in treatment become meaningless.

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Introduction:

Acute Lymphoblastic Leukemia (ALL) is the most common type of cancer in childhood. In recent years, new potential therapeutic targets have been found to understand leukemogenesis's genetic and molecular structure better. Options such as new generation monoclonal specific antibodies, bispecific antibodies, small molecule inhibitors, chimeric antigen receptor (CAR) T-cells have been added to treatment protocols.[1] By evaluating pharmacokinetic and pharmacodynamic properties, survival in ALL patients has increased to 90% in developed countries with personalized treatment methods. In the United States, an average of 3000 children are diagnosed with ALL every year, and long-term survival has increased to 85%-90% with current treatment methods.[2-5] The interaction of study groups and the development of increased risk-adapted treatment protocols over time, the addition of delayed intensification with vincristine, L-asparaginase, dexamethasone, and high-dose or escalating-dose methotrexate significantly improved the prognosis.[6-9] With the addition of imatinib-mesylate to treatment int(9:22) BCR-ABL positive (Ph-positive) leukemias, 5-year survival in Ph-positive ALL patients has increased from 27% to 80%.[10]

As a result, the struggle and the point reached in pediatric ALL treatment from the 1970s to the present time is a true success story. However, there is still a long way to go. In the last 15-20 years, excellent results have been achieved with intensive multi-agent chemotherapeutic regimens and risk-adjusted therapy that includes stem cell transplantation and adequate supportive care for a high-risk subset of patients.[11, 12] In patients with ALL, levels of minimal residual disease are indicative of the collective effect of leukemic cell genetics, microenvironment, host factors, and chemotherapy potency on treatment response.[13] The results of recent studies have shown that minimal residual disease (MRD) can be used to identify patients who can be successfully treated with low-intensity regimens, as well as those who need intensive therapy to reduce the risk of relapse.[14] The St Jude Total Therapy Study XV was the first clinical trial to use MRD levels prospectively during and after remission induction therapy to guide risk-directed treatment.[15] There were two crucial innovations in the Total Therapy XV study. These are the complete elimination of prophylactic cranial irradiation and the use of MRD to guide treatment. The use of MRD to guide treatment decisions in Total Therapy Study XV contributed significantly to the study's overall results by identifying patients with poor early treatment response and possibly benefiting from additional intensified treatment.

We used the Total Therapy XV protocol with minimal modification in the treatment of ALL patients in our center (a university hospital) in Istanbul, the most populous city of Turkey, where the majority of the patients are low and middle-income groups. In this study, we aimed to present the results of our pediatric patients treated with modified St Jude Total Therapy XV and examine our mortality rates, causes, and risk factors.

Material and Method:

Our study included pediatric ALL patients treated with the modified St Jude Total Therapy XV (Total XV) protocol during January 2011- December 2018, aged 1-18 years, who were diagnosed, and completed all the treatment in our hospital and followed up without interrupting their follow-up. Patients who were younger than 12 months of age at the time of admission, biphenotypic feature, had previous diagnoses such as myelodysplastic syndrome and Fanconi aplastic anemia, had previously received chemotherapy for other reasons, relapsed ALL patients, patients who did not come for regular follow-ups, continued their treatment in other centers and the patients who came to our hospital from other centers were excluded from the study. Again, the study did not include patients with mature B-cell (Burkitt) leukemia with different treatment protocols.

For the diagnosis of ALL, bone marrow aspiration was performed to evaluate the morphological findings in the staining of slides with Giemsa. Also, a 10 mL sample was taken from the bone marrow into an ethylenediaminetetraacetic acid (EDTA) tube, and cell surface markers of the blastic population were studied with flow cytometry (BD FACSCanto, BD Biosciences USA). Blastic cell populations for over 25% with flow cytometry were also diagnosed as ALL.

To classify risk groups, FISH and PCR methods were used to analyses and evaluate t(9;22) (q34;q11.2); BCR_ABL, t(12;21) (p13;q22); TEL-AML1 (ETV6-RUNX1), t(1;19) (q23;p13.3); TCF3-PBX1, t(v;11q23) (MLL rearranged) regions and chromosome analysis was performed via karyotyping. Patients were classified initially into three risk groups according to St Jude's Total XV protocol risk criteria based on patient age and leucocyte count at baseline and leukemic cell phenotype and genotype. The risk status of the patients was changed according to the level of minimal residual disease during and after remission induction therapy. Patients with 1% or higher minimal residual disease on day 19 of remission induction or between 0.01% and 0.99% on day 46 were included in the standard-risk ALL group. Patients with minimal residual disease of 1% or higher following completion of remission induction or 0.1% or higher on week 7 of maintenance treatment were included in the high-risk ALL group.

The patients were treated with the St Jude Children's Research Hospital Total XV protocol [15] with a minor modification. (The only modification was methylprednisolone 20 mg/kg/day for 7 days, 10 mg/kg/day for the second 7 days, and 2 mg/kg/d for other days instead of prednisolone 40 mg/m2/day orally in the induction phase).[16]

The chemotherapy regimens of all risk groups are summarized in a supplementary file.

CNS prophylaxis consisted of triple intrathecal therapy (MTX, cytarabine, and prednisolone), irrespective of the CNS status and the risk group; the total doses administered were based on the CNS status and the risk classification and ranged from 13 to 25. The number of intrathecal therapy doses administered was 13 for LR cases and ranged from 16 to 25 for IR/HR cases. None of our patients had refractory CNS leukemia and did not require cranial irradiation.

During treatment, all patients were given trimethoprim-sulfamethoxazole for Pneumocystis jirovechii prophylaxis, while patients with invasive fungal infections were given voriconazole prophylaxis until the end of their treatment. International febrile neutropenia protocols were used during febrile neutropenia periods, and all patients during febrile neutropenia periods were hospitalized and given broad-spectrum antibiotics and, if necessary, antifungal and antiviral treatments.[17, 18]

If there is an eligible donor, stem cell transplantation was performed on patients in the HR group or those with MRD positivity at week 7 on continuation treatment.

MRD studies

Minimal residual disease levels were measured in bone marrow specimens by multiparameter flow cytometry on days 19 and 46 of remission induction and weeks 7, 17, 48, and 120 (end of treatment for girls) or 146 (end of treatment for boys) of maintenance treatment. The leukemia markers that were used to study minimal residual disease by multiparameter flow cytometry are listed in Table 2.

Data of patients were retrospectively collected using the medical records in the electronic file system (MEDIN HBYS, Erguvan Information Technologies, Turkey) for five years, and age, gender, risk group, cell type, course of the disease, and follow-up period were recorded electronically (Microsoft Office 2013 package program Excel, Microsoft USA). Statistical analysis was done with SPSS 20.0 package program (IBM USA).

After finishing their treatment plan, patients continued to follow-up evaluations in the pediatric hematology outpatient policlinic every month during the first 6 months, every other month for the second 6 months, every three months for the next two years, every 6 months for five years, and then annually thereafter.

As appropriate, comparisons between categorical variables were carried out using either the Pearson-X^2 test or Fisher exact test. The duration of event-free survival (EFS) was calculated from the first day of treatment to the time of analysis (September 2021) or to the first event (early death, relapse, or death during remission). EFS and overall survival (OS) rates were estimated using the Kaplan-Meier method, and the survival curve was arranged in the SPSS 20.0 for Windows (SPSS Inc., Chicago, IL). The Mantel-Cox (Log Rank) test was used to analyze the factors affecting mortality. A P-value <0.05 was considered statistically significant.

The study was approved by the institutional ethics committee, and written informed consent was obtained from parents or guardians at the beginning of treatment.

Results:

A total of 115 patients, 70 male and 45 females (male/female: 1.56), were included in the study. The median follow-up period was 70 months. The gender and age characteristics, the mean initial laboratory values, and blast cell phenotypes of the patients according to risk groups are summarized in Table3.

One hundred three (89.6%) children had a pre–B-cell phenotype, 12 (10.4%) had a T-cell phenotype. According to the Total Therapy XV risk stratification criteria, 32 (27.8%) children were classified as low risk (LR), 63 (54.8%) as standard risk (SR), and 20 (17.4%) as high risk (HR).

Treatment Results

All 112 (97.4%) of the patients who completed remission induction therapy and whose BM could have been investigated at the remission date were in remission. Three (2.6%) children died in the induction period before the remission date.

Considering all patients, at a mean follow-up of 68 months (range, 1 to 115 mo), 5-year OS was 80%, (mean follow-up time 94.5 months, 95% CI 86.5-102), and EFS was 78.3% (mean 93.3 months, 95% CI 85.7-100.1).

Evaluation of survival according to gender showed that 5-year OS was 84.3% in boys and 73.3% in girls (98.7 months, 95% CI: 89.8-107.6 and 87, 95% CI: 73.9-100.2) 5-year OS rates were 78.1, 81%, and, 80% for the LR, SR, and HR groups, respectively. 5-year EFS rates were 75.9%, 79.4%, and 78.3% for the LR, SR, and HR groups, respectively. There was no significant difference between the groups according to the risk stratification (p=0.95). In the evaluation of survival according to the cellular origin, survival was 80.6% in the B-cell group (n=103) 95.1 (95% CI 87.3-103), and 75% in the T-cell group (n= 12) (70.8 months, 95% CI 50-91.6) OS was 82.1% in the group with baseline WBC <50,000 cells/mm3 while it was 70% in the group>50,000 cells/mm3 (n=20). However, there was no statistically significant difference due to the small number of patients (p=0.1). When we took the threshold value of 100,000 cells/mm3 for the initial WBC value, the difference became more evident. We observed OS was 82.4% in the WBC <100,000 group (n=102) vs 61.5% in WBC[?]100,000 cell/mm3 group (n=13) (p=0.56).

When the results were evaluated according to the age of onset, OS was 82.7% in the 1-9.99 age group (n=98) and was 64.7% in the group over ten years old (n=17). (p=0.07) We attribute the statistical insignificance of these rates to the low number of patients in the second (>10 age) group. But when we look at the EFS rates, we see a statistically significant difference in patients over 10 years old. The EFS was 81.6% in the 1-9.99 age group (n=98) and was 58.8% in the group over ten years old (n=17). (p=0.035)

Of the eight patients whose cytogenetic features could not be determined, four died. Although small in number (n=4), all patients with t (1;19) TCF3-PBX1 mutation survived, while all patients with hypodiploid (n=3) karyotyping died.

Three (2.6%) of patients had bone marrow relapses. (pre-B or T cell) All of these patients had been treated with relapse ALL protocols, and one of them had no response to treatment and died due to progressive disease. In the other two patients, remission was achieved with the relapse protocol, and then stem cell transplantation was performed. These two patients were still alive for 20 and 48 months after relapsing. Only one patient (0.87%) developed an isolated CNS relapse, and he was cured with a bone marrow transplantation from his brother after relapse chemotherapy treatment. Ten of our patients underwent SCT. Four of them were due to MRD positivity detected on the 46th day.

When the causes of death of our patients were examined, it was seen that 19 of the 23 patients died due to infection and infection-related complications [three patients (2.61%)] died in the induction phase, and 16 (13.91%) died due to infectious cause while in remission), two patients died due to progressive, disease, and two patients died due to HSCT complications.

Discussion:

Survival rates in children with ALL have significantly improved over the years. The 5-year survival rate of 93.5% for St Jude's Total Therapy 15 is an excellent example of the significant advances in treatment.[19] Especially in High-Income Counties (HIC), risk groups are well defined; nutritional problems are less severe, supportive care conditions are better, hygienic conditions are more suitable, the ratio of health care personnel per patient is high, access to drugs is faster than Low-Income Countries (LIC) thus reducing treatment-related death (TRD, TRM) rate to 1%. Unfortunately, survival rates from low and middle-income countries are not as reasonable as HIC and range from 30 to 70% for various risk groups [20-22]; and TRD rate is observed at the level of 11-21%. Poor outcomes may result from lack of adequate supportive care, poor management of fulminant infections, elevated costs of health care and financial problems, compliance issues, the inability to apply current standard treatment protocols, and host factors.

Our results showed that the high remission and low relapse rates of our patients are pretty satisfactory. All of the patients who completed induction therapy were in remission at the remission date. Only three patients had bone marrow relapses, and one had CNS relapse. But the high number of patients lost due to infectious diseases caused relatively low OS and EFS.

An overlooked point in evaluating treatment efficacy is treatment continuity. Gupta et al., in a meta-analysis including middle-income countries, have shown that the treatment dropout rate had a wide range of 0-74.5%. There was not any treatment dropout in our patients.[23]

According to 2019 data, our country is among the Upper Middle-Income Countries (WorldBank -WB). Due to the location of our hospital, most of our patients come from low- and middle-income segments of the Turkish population. According to our study results, our patients' OS, EFS, and TRD results are seen between developing and developed countries. According to WB 2010 data, 83% of the world's population lives in low- and middle-income countries. In these countries, the ratio of the child population to the total population is also higher than in high-income countries (Low-income 40%, Middle-income: 27%, and high-income: 17%).[24]

In most clinical studies, boys appear to have worse outcomes than girls when given equal treatment.[25, 26] However, in our study, OS was 84.3% in boys and 73.3% in girls. (p=0.16). In our study, we found that the biggest problem that caused the decrease in the survival of our patients was the deaths caused by infectious diseases while the patients were in remission.

In addition to the risk criteria that predict relapse, measurement of early responses to therapy and the extent of MRD studies at various time points in induction, consolidation, and continuation can significantly improve the accuracy of risk assessment.[27] In our study, MRD measurement was performed on days 19 and 46 of remission induction, and on weeks 7, 17, 48, and at the end of the maintenance treatment by using multicolor flow cytometry, and patients with positive MRD results were referred to SCT.

Yetgin et al.[16] reported that high-dose methylprednisolone (HDMP) has a higher cure rate, prolonged remission duration, and EFS rate, and higher long-term effectiveness compared to the conventional dose prednisolone administration used in ALL induction therapy. Therefore, the St Jude Total Therapy XV protocol was used with this minor modification.

In this study, CNS prophylactic therapy consisted of triple intrathecal therapy without prophylactic cranial radiation in contrast to previous Total Therapy studies. Previous study results reported that intensive intrathecal therapy for HR groups eliminated the need for prophylactic cranial radiation.[12] In our study, only one patient (0.87%) had isolated CNS relapse) Furthermore, this result supports that triple intrathecal therapy without cranial radiation is very effective as CNS prophylaxis.

When we examined the mortality times of our patients, only three patients (2.61%) died in the induction phase, and they died due to infectious causes. According to literature data, mortality at the start of treatment or induction period constitutes one-tenth of all mortality or half of treatment-related mortality.[28] From this point of view, it is seen that our data is compatible with the literature. Again, as an example of lower-middle-income countries, Khan et al. from Pakistan published a study that emphasized the induction period mortality was 20.8% in 48 newly diagnosed patients between 2014-15, and that hemorrhage/bleeding complications were the cause of death in half of these patients, while infection and related complications were the cause of death in 40%.[29] This article points out how essential it is to access blood products and the adequacy of blood centers. In our study, no patient died due to bleeding alone. However, five patients died (4.35% of all patients, 21.75% of all mortality) due to disseminated intravascular coagulation (DIC) accompanied by bleeding. These findings were valuable in showing how vital infection prevention is. Diba et al. published their ALL study in Bangladesh (lower middle income – WB) involving 87 children aged 1-18 years that the cumulative mortality was found to be 29.9%, and the primary cause of death (22/26, 84.6%) was septicemia.[30]

Infection is not just a problem of LICs. Although the mortality rate is low when examined in HIC, infection, and septicemia are still the number one cause among the causes of TRD. Lund et al. published a study in 2011 that reported TRD as 3.4% and 3.2% in the NOPHO ALL-92 and ALL-2000 protocols. They pointed out that the primary reason for TRD was infection (73%).[31] Hao et al. retrospectively analyzed a total of 238 children with ALL who were followed up between 2008 and 2018 and reported 74 deaths (cumulative mortality 31.1%). The primary reason for this rate, which seems to be relatively high in today's conditions,

is infection and related conditions (43.2%). Another interesting result in the same study is that the mortality of male patients is more than twice as high (73% vs. 27%) compared to female patients.[32] It is known that mortality is slightly higher in males. However, such a high difference is not reported in the literature.[2, 33-35] In our study, cumulative mortality was 20%, and OS was higher in males, contrary to the literature (84.3% vs. 73.3%). Another study that finds female gender as a risk factor for TRDs is Lund et al.'s study.[31]

It is clear that with the increase in income, the conditions of care improve, the access to supportive treatments becomes more accessible, and the hygiene conditions are of better quality.[31] The effect of income level on treatment is felt in different regions of the same country. Koc et al., in the article they published in 2013, found OS 77.4% and EFS 68.9% in the Southeastern Anatolia Region of Turkey, which has a lower income level compared to the Marmara Region, where our patient population is located. They reported 12.3% mortality in the remission induction phase.[36] Again, Ozturk et al. reported a 5- and 10-year OS as 85.9% in their retrospective review of 98 patients treated in Istanbul between 1999 and 2014. Significant causes of death were found to be infection complications and other TRDs.[37]

Study results of various clinical trial groups are summarized in Table 5.

Physicians, the pharmaceutical industry, scientists, politicians, international health and economic organizations should make childhood ALL a treatable disease without morbidity. Another issue that is at least as necessary as this should be the policy of equality in health. It is the undisputed right of every child to have optimal health conditions, treatment, and care services. Ensuring these conditions is everyone's moral responsibility. Under the leadership of international organizations such as WHO, IMF, WB, and developed country managers, we must fight with all our strength to provide all children of the world with the 90-95% survival rates they deserve in ALL treatment, regardless of their income level.

Conclusion:

Our study results supported the data that performing CNS prophylaxis with triple intrathecal therapy in pediatric patients with ALL and early recognition of patients with a high probability of relapse with MRD follow-ups increase patient survival rates. However, improving treatment protocols and early detection of patients with a high probability of relapse alone are not sufficient to increase survival rates, especially in developing countries. In order to prevent deaths due to infections in LICs, it is necessary to take social and economic measures as well as medical studies.

Special thanks: The authors thank the esteemed Dr. C-H Pui for sharing your valuable opinions with us.

References

1. Kaplan JA: Leukemia in Children. Pediatr Rev 2019, 40(7):319-331.

2. Gaynon PS, Angiolillo AL, Carroll WL, Nachman JB, Trigg ME, Sather HN, Hunger SP, Devidas M, Children's Oncology G: Long-term results of the children's cancer group studies for childhood acute lymphoblastic leukemia 1983-2002: a Children's Oncology Group Report. Leukemia 2010, 24(2):285-297.

3. Maloney KW, Devidas M, Wang C, Mattano LA, Friedmann AM, Buckley P, Borowitz MJ, Carroll AJ, Gastier-Foster JM, Heerema NA et al: Outcome in Children With Standard-Risk B-Cell Acute Lymphoblastic Leukemia: Results of Children's Oncology Group Trial AALL0331. J Clin Oncol 2020, 38(6):602-612.

4. Pui CH, Mullighan CG, Evans WE, Relling MV: Pediatric acute lymphoblastic leukemia: where are we going and how do we get there? Blood 2012, 120(6):1165-1174.

5. Surapolchai P, Anurathapan U, Sermcheep A, Pakakasama S, Sirachainan N, Songdej D, Pongpitcha P, Hongeng S: Long-Term Outcomes of Modified St Jude Children's Research Hospital Total Therapy XIIIB and XV Protocols for Thai Children With Acute Lymphoblastic Leukemia. Clin Lymphoma Myeloma Leuk 2019, 19(8):497-505.

6. Attarbaschi A, Mann G, Zimmermann M, Bader P, Barisone E, Basso G, Biondi A, Cario G, Cazzaniga G, Colombini A et al: Randomized post-induction and delayed intensification therapy in high-risk pediatric acute lymphoblastic leukemia: long-term results of the international AIEOP-BFM ALL 2000 trial. Leukemia 2020, 34(6):1694-1700.

7. Pui CH, Relling MV, Sandlund JT, Downing JR, Campana D, Evans WE: Rationale and design of Total Therapy Study XV for newly diagnosed childhood acute lymphoblastic leukemia. Ann Hematol 2004, 83 Suppl 1:S124-126.

8. Quist-Paulsen P, Toft N, Heyman M, Abrahamsson J, Griškevičius L, Hallböök H, Jónsson ÓG, Palk K, Vaitkeviciene G, Vettenranta K et al: T-cell acute lymphoblastic leukemia in patients 1–45 years treated with the pediatric NOPHO ALL2008 protocol. Leukemia 2020, 34(2):347-357.

9. Vora A, Goulden N, Wade R, Mitchell C, Hancock J, Hough R, Rowntree C, Richards S: Treatment reduction for children and young adults with low-risk acute lymphoblastic leukaemia defined by minimal residual disease (UKALL 2003): a randomised controlled trial. Lancet Oncol 2013, 14(3):199-209.

10. Schultz KR, Carroll A, Heerema NA, Bowman WP, Aledo A, Slayton WB, Sather H, Devidas M, Zheng HW, Davies SM et al: Long-term follow-up of imatinib in pediatric Philadelphia chromosome-positive acute lymphoblastic leukemia: Children's Oncology Group Study AALL0031. Leukemia 2014, 28(7):1467-1471.

11. Balduzzi A, Valsecchi MG, Uderzo C, De Lorenzo P, Klingebiel T, Peters C, Stary J, Felice MS, Magyarosy E, Conter V et al: Chemotherapy versus allogeneic transplantation for very-high-risk childhood acute lymphoblastic leukaemia in first complete remission: comparison by genetic randomisation in an international prospective study. Lancet 2005, 366(9486):635-642.

12. Pui CH, Pei D, Sandlund JT, Ribeiro RC, Rubnitz JE, Raimondi SC, Onciu M, Campana D, Kun LE, Jeha S et al: Long-term results of St Jude Total Therapy Studies 11, 12, 13A, 13B, and 14 for childhood acute lymphoblastic leukemia. Leukemia 2010, 24(2):371-382.

13. Campana D: Minimal residual disease monitoring in childhood acute lymphoblastic leukemia. Curr Opin Hematol 2012, 19(4):313-318.

14. Bader P, Salzmann-Manrique E, Balduzzi A, Dalle J-H, Woolfrey AE, Bar M, Verneris MR, Borowitz MJ, Shah NN, Gossai N et al: More precisely defining risk peri-HCT in pediatric ALL: pre- vs post-MRD measures, serial positivity, and risk modeling. Blood Advances 2019, 3(21):3393-3405.

15. Pui C-H, Campana D, Pei D, Bowman WP, Sandlund JT, Kaste SC, Ribeiro RC, Rubnitz JE, Raimondi SC, Onciu M et al: Treating Childhood Acute Lymphoblastic Leukemia without Cranial Irradiation. New England Journal of Medicine 2009, 360(26):2730-2741.

16. Yetgin S, Tuncer MA, Çetin M, Gümrük F, Yenicesu I, Tunç B, Öner AF, Toksoy H, Koç A, Aslan D et al: Benefit of high-dose methylprednisolone in comparison with conventional-dose prednisolone during remission induction therapy in childhood acute lymphoblastic leukemia for long-term follow-up. Leukemia 2003, 17(2):328-333.

17. Manji A, Lehrnbecher T, Dupuis LL, Beyene J, Sung L: A systematic review and meta-analysis of anti-pseudomonal penicillins and carbapenems in pediatric febrile neutropenia. Supportive Care in Cancer 2012, 20(10):2295-2304.

18. Petty LA, Sokol EA, Bartlett AH, McNeer JL, Alexander KA, Pisano J: Repeated Blood Cultures in Pediatric Febrile Neutropenia: Would Following the Guidelines Alter the Outcome? Pediatric Blood & Cancer 2016, 63(7):1244-1249.

19. Pui CH, Pei D, Coustan-Smith E, Jeha S, Cheng C, Bowman WP, Sandlund JT, Ribeiro RC, Rubnitz JE, Inaba H et al: Clinical utility of sequential minimal residual disease measurements in the context of risk-based therapy in childhood acute lymphoblastic leukaemia: a prospective study. Lancet Oncol 2015, 16(4):465-474.

20. Gao YJ, Lu FJ, Wang HS: Treating childhood acute lymphoblastic leukemia in a developing country 1998-2003: the experience of a single children's hospital in China. J Pediatr Hematol Oncol 2006, 28(12):798-802.

21. Howard SC, Pedrosa M, Lins M, Pedrosa A, Pui C-H, Ribeiro RC, Pedrosa F: Establishment of a Pediatric Oncology Program and Outcomes of Childhood Acute Lymphoblastic Leukemia in a Resource-Poor Area. JAMA 2004, 291(20):2471-2475.

22. Liang DC, Yang CP, Lin DT, Hung IJ, Lin KH, Chen JS, Hsiao CC, Chang TT, Peng CT, Lin MT et al: Long-term results of Taiwan Pediatric Oncology Group studies 1997 and 2002 for childhood acute lymphoblastic leukemia. Leukemia 2010, 24(2):397-405.

23. Gupta S, Yeh S, Martiniuk A, Lam CG, Chen HY, Liu YL, Tsimicalis A, Arora RS, Ribeiro RC: The magnitude and predictors of abandonment of therapy in paediatric acute leukaemia in middle-income countries: a systematic review and meta-analysis. Eur J Cancer 2013, 49(11):2555-2564.

24. Magrath I, Steliarova-Foucher E, Epelman S, Ribeiro R, Haraif M, Chi-Kong L, Rejin K: Improving cancer care for children and young people 2. Lancet Oncol 2013, 13:104-116.

25. Pui CH, Boyett JM, Relling MV, Harrison PL, Rivera GK, Behm FG, Sandlund JT, Ribeiro RC, Rubnitz JE, Gajjar A et al: Sex differences in prognosis for children with acute lymphoblastic leukemia. J Clin Oncol 1999, 17(3):818-824.

26. Shuster JJ, Wacker P, Pullen J, Humbert J, Land VJ, Mahoney DH, Jr., Lauer S, Look AT, Borowitz MJ, Carroll AJ et al: Prognostic significance of sex in childhood B-precursor acute lymphoblastic leukemia: a Pediatric Oncology Group Study. J Clin Oncol 1998, 16(8):2854-2863.

27. Sutton R, Venn NC, Tolisano J, Bahar AY, Giles JE, Ashton LJ, Teague L, Rigutto G, Waters K, Marshall GM: Clinical significance of minimal residual disease at day 15 and at the end of therapy in childhood acute lymphoblastic leukaemia. British journal of haematology 2009, 146(3):292-299.

28. Seif AE, Fisher BT, Li Y, Torp K, Rheam DP, Huang Y-SV, Harris T, Shah A, Hall M, Fieldston ES et al: Patient and hospital factors associated with induction mortality in acute lymphoblastic leukemia. Pediatric Blood & Cancer 2014, 61(5):846-852.

29. Khan MI, Naseem L, Manzoor R, Yasmeen N: Mortality analysis in children during induction therapy for acute lymphoblastic leukemia. JIMDC 2017, 6(2):69-72.

30. Diba F, Karim MA, Soma SA, Chowdhury I, Mamun S, Mondal MNI: Immunophenotypic Pattern and Treatment Outcome after Completion of Induction Remission in Children with Acute Lymphoblastic Leukemia. Journal of Current and Advance Medical Research 2021, 8(1):59-64.

31. Lund B, Åsberg A, Heyman M, Kanerva J, Harila-Saari A, Hasle H, Söderhäll S, Jónsson ÓG, Lydersen S, Schmiegelow K et al: Risk factors for treatment related mortality in childhood acute lymphoblastic leukaemia. Pediatric Blood & Cancer 2011, 56(4):551-559.

32. Kiem Hao T, Nhu Hiep P, Kim Hoa NT, Van Ha C: Causes of Death in Childhood Acute Lymphoblastic Leukemia at Hue Central Hospital for 10 Years (2008-2018). Global Pediatric Health 2020, 7:2333794X20901930.

33. Escherich G, Horstmann MA, Zimmermann M, Janka-Schaub GE, on behalf of the Csg: Cooperative study group for childhood acute lymphoblastic leukaemia (COALL): long-term results of trials 82,85,89,92 and 97. Leukemia 2010, 24(2):298-308.

34. Gupta S, Antillon FA, Bonilla M, Fu L, Howard SC, Ribeiro RC, Sung L: Treatment-related mortality in children with acute lymphoblastic leukemia in Central America. Cancer 2011, 117(20):4788-4795.

35. Reiter A, Schrappe M, Ludwig W, Hiddemann W, Sauter S, Henze G, Zimmermann M, Lampert F, Havers W, Niethammer D: Chemotherapy in 998 unselected childhood acute lymphoblastic leukemia patients.

Results and conclusions of the multicenter trial ALL-BFM 86. Blood 1994, 84(9):3122-3133.

36. Koc A, Aycicek A, Ozdemir ZC, Soker M, Varma M: Outcome of modified St Jude total therapy 13A for childhood acute lymphoblastic leukemia in the southeast region of Turkey. Journal of pediatric hematology/oncology 2013, 35(1):36-41.

37. Öztürk AP, Koç B, Zülfikar B: Acute Complications and Survival Analysis of Childhood Acute Lymphoblastic Leukemia: A 15-year Experience. Clinical Lymphoma Myeloma and Leukemia 2021, 21(1):e39-e47.

38. Conter V, Aricò M, Basso G, Biondi A, Barisone E, Messina C, Parasole R, De Rossi G, Locatelli F, Pession A et al: Long-term results of the Italian Association of Pediatric Hematology and Oncology (AIEOP) Studies 82, 87, 88, 91 and 95 for childhood acute lymphoblastic leukemia. Leukemia 2010, 24(2):255-264.

39. Möricke A, Zimmermann M, Reiter A, Henze G, Schrauder A, Gadner H, Ludwig W-D, Ritter J, Harbott J, Mann G et al: Long-term results of five consecutive trials in childhood acute lymphoblastic leukemia performed by the ALL-BFM study group from 1981 to 2000. Leukemia : official journal of the Leukemia Society of America, Leukemia Research Fund, UK 2009, 24:265-284.

40. Harms DrO, Gobel U, Spaar HJ, Graubner UB, Jorch N, Gutjahr P, Janka-Schaub GE, Group ftCS: Thioguanine offers no advantage over mercaptopurine in maintenance treatment of childhood ALL: results of the randomized trial COALL-92. Blood 2003, 102(8):2736-2740.

41. Kamps WA, van der Pal-de Bruin KM, Veerman AJP, Fiocco M, Bierings M, Pieters R: Long-term results of Dutch Childhood Oncology Group studies for children with acute lymphoblastic leukemia from 1984 to 2004. Leukemia 2010, 24(2):309-319.

42. Vrooman LM, Stevenson KE, Supko JG, O'Brien J, Dahlberg SE, Asselin BL, Athale UH, Clavell LA, Kelly KM, Kutok JL et al: Postinduction dexamethasone and individualized dosing of Escherichia Coli L-asparaginase each improve outcome of children and adolescents with newly diagnosed acute lymphoblastic leukemia: results from a randomized study–Dana-Farber Cancer Institute ALL Consortium Protocol 00-01. J Clin Oncol 2013, 31(9):1202-1210.

43. Gustafsson G, Schmiegelow K, Forestier E, Clausen N, Glomstein A, Jonmundsson G, Mellander L, Mäkipernaa A, Nygaard R, Saarinen-Pihkala U: Improving outcome through two decades in childhood ALL in the Nordic countries: the impact of high-dose methotrexate in the reduction of CNS irradiation. Leukemia 2000, 14(12):2267-2275.

44. Toft N, Birgens H, Abrahamsson J, Griškevičius L, Hallböök H, Heyman M, Klausen TW, Jónsson Ó, Palk K, Pruunsild K et al: Results of NOPHO ALL2008 treatment for patients aged 1–45 years with acute lymphoblastic leukemia. Leukemia 2018, 32(3):606-615.

45. Pui CH, Pei D, Campana D, Cheng C, Sandlund JT, Bowman WP, Hudson MM, Ribeiro RC, Raimondi SC, Jeha S et al: A revised definition for cure of childhood acute lymphoblastic leukemia. Leukemia 2014, 28(12):2336-2343.

46. Hough R, Rowntree C, Goulden N, Mitchell C, Moorman A, Wade R, Vora A: Efficacy and toxicity of a paediatric protocol in teenagers and young adults with Philadelphia chromosome negative acute lymphoblastic leukaemia: results from UKALL 2003. Br J Haematol 2016, 172(3):439-451.

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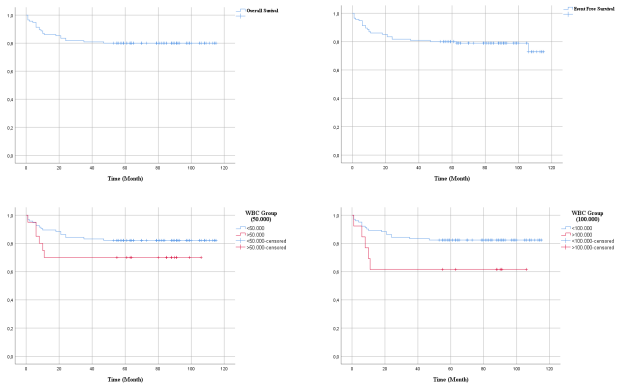

Figure 1: Survival curves of patients according to various characteristics. a) OS 80% b) EFS 78.3 c) WBC group (50.000) (p=0.19) d) WBC group (100.000) (p=0.056)

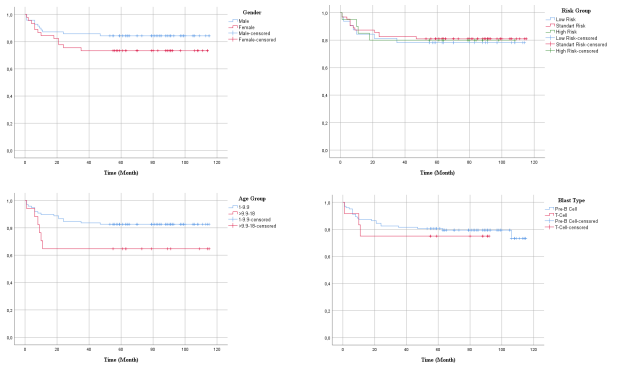

Figure 2: Survival curves of patients according to various characteristics. a) Gender (p=0.16) b) Risk group (p=0.94) c) Age group (p=0.07) d) Blast type (p=0.67)