IMPROVED SURVIVAL FOR CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA IN A LOW MIDDLE-INCOME COUNTRY: REDUCTION IN ABANDONMENT and relapse

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Abstract

Background: In our earlier published outcomes of children with acute lymphoblastic leukemia (ALL) at Moi Teaching and Referral Hospital in Kenya (MTRH), we showed low event-free survival (EFS) with high induction mortality and abandonment. Based on this observation, the team focused on strategies to reduce both causes of poor outcomes. **Intervention:** We dropped doxorubicin from induction therapy as the supply of L-asparaginase became reliable, improved social and financial support for insurance coverage and transportation, promptly initiated empirical antibiotics during episodes of febrile neutropenia, and enhanced the availability of blood products. **Objective:** Our study compared childhood ALL outcomes before (2010-2016) and after (2017-2020) modification of induction therapy, with improved social and financial support and supportive care. **Methods:** We reviewed the medical records of 123 children with ALL between 2017 to 2020. Their treatment results were collected and compared to those of 136 children before the (2010-2016) modification of induction therapy, with improved social and financial support. **Results:** Three-year EFS estimates improved from 18.2% to 40.7%. Relapse or progressive disease decreased from 26% to 16%, and abandonment from 24% to 14%. Deaths and survival through induction did not change significantly between the two periods. Children between 1-9 years and those with white blood cell (WBC) count $<50\text{x}10^{9}$/L had better EFS. **Conclusions:** Treatment abandonment and relapse decreased, and EFS increased significantly. However, strategies to improve early diagnosis and supportive care are needed to reduce induction mortality. In addition, enhanced parental education and continuous counseling are required to minimize treatment abandonment further.

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is globally the most common childhood malignancy. [1] Survival of childhood ALL has improved significantly in high-income countries (HIC) with over 90% 5-year overall survival (OS), while low-middle-income countries (LMIC) continue to register dismal survival rates.[2-6] In sub-Saharan Africa, 2-year event-free survival estimates of 22% and 33% have been reported in Rwanda and Tanzania, respectively.[7-8] The poor outcomes of childhood ALL in LMICs are characterized by high induction mortality, treatment abandonment, and leukemia relapse.[3,6,7] These poor outcomes are associated with low socioeconomic status, delayed diagnosis and treatment, and inadequate medical resources to support the patients.[4-6]

Since 2010, in collaboration with twining partners from Princess Máxima Center for Pediatric Oncology in the Netherlands and Indiana University in the United States of America (USA), we have been treating children with ALL using resource-adapted protocols. The previously published treatment outcome of children with ALL in our setting between 2010 to 2016 showed low event-free survival associated with high induction mortality and abandonment rates.[9] Following this observation, our team came up with strategies to reduce induction deaths and abandonment.

In this study, we compared childhood ALL outcomes before (2010-2016) and after the (2017-2020) modification of induction therapy with improved social and financial support and supportive care.

METHODS

Setting

Kenya is a low-middle-income country (LMIC) with an estimated population of 55 million as of 2021, according to world bank data. The population below the poverty line is estimated at 36.1% as of 2015. Children below the age of 15 accounts for 39% of the total population.[10-12]

Over 80% of the Kenyan population does not have health insurance coverage. The National Health Insurance Fund (NHIF) is the primary insurer covering approximately 16 %, while private insurers cover about 1% of the Kenyan population. This leaves most Kenyans paying hospital bills out of pocket.[13] The study was carried out at MTRH, the country's second-largest public hospital that offers pediatric cancer treatment. It is situated in the western part of the country, in Eldoret town, Uasin Gishu county. It serves a catchment population of about 25 million people. On average, 240 children were diagnosed with cancer annually during the period in review. The pediatric oncology unit has a capacity of thirty-five beds with a bed occupancy of over 200%. Most patients begin their initial treatment in the general wards before being transferred to the oncology unit. The children with cancer are cared for by a multidisciplinary team in collaboration with visiting pediatric hematology-oncology experts from our twinning partner institutions in the Netherlands and the USA.

Intervention

In the previous (2010-2016) cohort, doxorubicin was used in the induction therapy (6 weeks). It was dropped in the current cohort (2017-2020) from the induction phase once the L-asparaginase supply was consistent. The patients received a three-drug induction (vincristine, prednisone, and L-asparaginase) lasting six weeks. Additionally, patients who did not have health insurance (NHIF) were supported to enroll and transport assistance for needy parents through collaboration with philanthropic organizations and continuous parental counseling and support groups. The social work department facilitated this. Supportive care included better availability and early initiation of antibiotics during episodes of febrile neutropenia and enhanced availability of blood products.

Study design

This was a retrospective medical records study of children (0-16 years) diagnosed with ALL at MTRH from January 2017 to December 2020. We included all children with a diagnosis of ALL, regardless of their clinical condition, before the initiation of treatment. Previous medical record data before (2010-2016) modification of induction therapy, with improved social and financial support and supportive care, was available for comparison.

Socio-demographic data, including age, gender, the distance of residence from MTRH, and duration of symptoms, had been collected at diagnosis for the current cohort (2017-2020) and was available. In addition, we obtained data on health insurance status and treatment outcomes from the medical records. We recorded treatment outcomes as abandonment, death, relapsed or progressive disease, and event-free. Additional clinical data for the current cohort (2017-2020) included: white blood cell (WBC) count at diagnosis, ALL immunophenotype, and central nervous system (CNS) disease status. We determined survival through induction and the survival estimates by WBC, sex, age at diagnosis, health insurance status (NHIF) at diagnosis,

event-free and overall survival.

The children with ALL at MTRH were treated with a modification of the Dutch Oncology Group ALL-6 Study (1984-1988) therapy for non-high-risk ALL.[14] All patients received the same standard protocol without risk stratification and consisted of induction (6 weeks), consolidation (2 weeks), methotrexate phase (7 weeks), re-induction (3 weeks), and maintenance therapy (83 weeks). For this cohort study (2017-2020), doxorubicin was dropped from the induction phase) as the supply of vincristine, prednisone, and especially L-asparaginase was improved. The additional modification included intensified L-asparaginase therapy and a fourth high-dose methotrexate. The duration of ALL treatment lasts for 104 weeks (supplementary material, TABLE S1).

The diagnosis of ALL was made based on a bone marrow examination by the pathologists. Due to financial constraints, the use of flow cytometry to further confirm the diagnosis and determine ALL immunophenotypes could only be done in some patients.

Refusal to start or continue with planned treatment for four or more weeks consecutively was considered treatment abandonment.[9,15] Induction or early deaths were those that occurred before the start of treatment or during induction (<42 days from the start of treatment).[3,9]Deaths that occurred before the start of treatment or following relapsed/progressive leukemia were deemed to be disease-related. The deaths that occurred after treatment was initiated were deemed to be treatment-related. The clinical signs and symptoms and the presence of lymphoblasts on bone marrow aspirate or peripheral blood smear confirmed the relapsed disease). CNS involvement was evaluated through cerebral-spinal fluid examination, which was reported as positive or negative.

This study was approved by the Institutional research and ethics committee of MTRH and Moi University.

Data analysis

Statistical analysis was performed using R version 4.1.2. Descriptive statistics were used to analyze patient demographics, clinical characteristics, and outcomes. Data are reported as medians and interquartile range (IQR) or means and standard deviation (SD)where applicable. Comparisons of variables between the earlier cohort and the current cohort were analyzed for significance using the chi-square test and t-test. Continuous variables were compared by the two-tailed chi-square test and Fisher's exact test where applicable. The level of significance was set for a p-value <0.05. Survival estimates were determined using the Kaplan-Meier method.

Event-free survival (EFS) was based on the time of diagnosis to the date of the first treatment outcome (death, relapse/progressive disease, abandonment, alive at last follow-up). Overall survival (OS)was based on the time of diagnosis until the patient's death or the last follow-up if alive. The analysis of prognostic factors was based on the EFS and the comparison of curves by the log-rank test.

RESULTS

From January 2010 to December 2016 (before the modification of induction therapy, with improved social and financial support), 136 medical records of children with ALL (0-16 years) had previously been reviewed and published, and data were available for comparison.

From January 2017 through December 2020 (after modification of induction therapy, with improved social and financial support), 160 children (0-16 years) were diagnosed with ALL at MTRH. Their data on age, sex, duration of illness, and distance to the hospital had been collected at diagnosis and was available. In addition, we retrieved medical records for 123 of the 160 children. We collected data on outcomes (relapse/progressive disease, death, abandonment of therapy, event-free survival), health insurance, WBC count at diagnosis, ALL immunophenotype, and CNS disease status.

Table 1 illustrates the socio-demographic and clinical characteristics of the two cohorts. There was no difference in age and sex distribution between the two cohorts before (n=136) and after (n=160) modification of induction therapy with improved social and financial support. The number of patients with no health

insurance (NHIF) decreased from 16% to 2% before (n=136) and after (n=123), respectively. Patients who had symptoms for 1-3 months were 68 (52%) and 72(45%) before (n=132) and after (n=156), respectively. The number of patients whose residence is >100 kilometers from MTRH increased from 60%(n=136) to 80%(n=157).

Table 2 shows the first treatment outcomes before (n=136) and after (n=123) the modification of induction therapy with improved social and financial support. Death, the most common cause of treatment failure in our setting, did not change significantly between the two periods. Most of the deaths were treatment-related in both periods. Abandonment decreased significantly between the two periods ($p<0.03318$). Most children abandoned treatment during maintenance therapy: 18 out of 33 in 2010-2016 (n=136) and 15 out of 17 in the 2017-2020 (n=123) period. Relapse/progressive disease decreased significantly ($p<0.04136$). Among children who had a relapse of their disease, it occurred during maintenance in 19(70%) and 12(67%) of them before (19/27) and after (12/18), respectively. Event-free survival increased significantly($p<0.00001$) between the two periods.

Figure 1 shows comparisons of survival through induction between the two periods. Patients who died in induction decreased from 24% (32/136) to 17% (21/123) between the two periods. However, the difference was not statistically significant ($p< 0.198$). Figure 2 shows the comparison of treatment abandonment between the two cohorts. Treatment abandonment decreased significantly from 24% to 14% ($p<0.03318$).

The sex, duration of symptoms, distance to the hospital, and health insurance status did not significantly influence treatment outcomes and event-free survival estimates in both cohorts. Patients with relapsed or progressive disease were offered palliative therapy, and all died. In the 2017- 2020 cohort alone (no data for the 2010-2016 cohort), out of 24 children with CNS disease, 14(58%) died, 4(17%) were referred for cranio-spinal radiation (there were no radiotherapy services at MTRH), 3(13%) were among those who abandoned treatment, and 4(17%) were still alive with enhanced intrathecal chemotherapy.

However, age and WBC count at diagnosis significantly influenced event-free survival in the 2017- 2020 cohort. Figure 3(A) shows event-free survival by WBC count at diagnosis. Patients with WBC count <50 x 10^9/L had better event-free survival compared to those with >50 x 10^9/L ($p<0.017$). Figure 3(B) shows that children between the age of 1 year to 9 years had better event-free survival, while those below one year of age had the worst outcome ($p<0.0001$).

Figure 4(A) compares event-free survival estimates between the two cohorts. The EFS at three years significantly improved from 18% (95%CI, 0.123-0.268) to 41% (95%CI, 0.319-0.518) ($p<0.0001$). Figure 4(B) shows the overall survival estimates for the 2017- 2020 cohort alone (no data for the old cohort). This cohort's 3-year overall survival (OS) estimate was 49.2% (95% CI, 39.1% to 62%).

DISCUSSION

This study shows a significant improvement in 3-year EFS estimates of children diagnosed with ALL at MTRH (from 18% to 41%). This could be attributed to a reduction in the abandonment of therapy and relapse. However, death was the most common cause of treatment failure, with a significant proportion of deaths occurring during induction in the two cohorts.

Treatment abandonment as a cause of treatment failure reduced significantly (from 27% to 14%) in this study. It is modestly lower than Honduras, 22% and Indonesia, 35%.[4-5] However, this was higher than observed in Pakistan, 7.5%, and Rwanda, 10%.[3,7] Abandonment has been directly associated with low socioeconomic status and long travel time in some LMICs.[3,6] Lack of medical insurance has been associated with higher rates of treatment abandonment and lower overall survival of cancer patients in previous studies in Kenya.[16] With most patients abandoning treatment during maintenance, it is probable that because patients look relatively well during maintenance, parents may think they are cured. The long duration of ALL treatment is also likely to cause families to become lethargic over time. The reduction in abandonment in this study can be attributed to continuous counseling of parents, assessing for the economic challenges, and mitigating them whenever possible. That includes assisting parents in enrolling in health insurance (NHIF) and parent

support groups by the social-work services department.

The relapsed leukemia decreased significantly as a first treatment outcome. Out of those that achieved remission, the proportion of children that had a relapse (19%) was similar to what has been found in other studies where relapses are reported to range between 12% and 20%.[17] Due to decreased abandonment, there were probably more patients at risk of relapse in this study. Like other centers in LMIC, our patients are treated with a standard treatment protocol without risk stratification. That means sub-optimal intensity post-induction therapy for high-risk ALL children and corresponding poor EFS. In Rwanda, in a study by Rubagumya et al. children with ALL who were treated with low-intensity treatment had EFS of 22%, with relapse as the leading cause of treatment failure (53%). However, treatment-related toxicity was acceptably low.[7]Therefore, there is a need to adopt a risk stratification criterion at MTRH, with more intensification of therapy for the high-risk group to reduce relapses.

Historically, WBC and age at diagnosis, sex, initial treatment response determined by end induction bone marrow morphological remission, and immunophenotype have been used to stratify patients' risk status and predict the outcome. In this study, we showed that ALL patients with an initial WBC $<50 \times 10^9$/L and patients in the age group 1 to 9 years had better event-free and overall survival with the current treatment protocol. Patients with CNS involvement were at high risk of death despite intensified intrathecal chemotherapy alone, as there were no radiotherapy services available during the period, and few patients were referred out for craniospinal radiation. Studies from HIC have shown that determination of end-induction measurable residual disease (MRD) by flow-cytometry or PCR has proven to be a reliable predictor for relapse and overall outcome. Post-induction treatment intensification for end-induction MRD-positive patients improved overall survival.[18,19] However, treatment intensification for high-risk patients demands more intensive supportive care that is not readily achievable in most centers in LMICs. Also, we do not have the resources to monitor MRD in our setting.

The proportion of patients who died during induction decreased (from 24% to 17%) between the two periods, although the difference was not statistically significant. Most of the deaths were treatment-related. These induction deaths approximate what was observed in other LMICs. In a study by Jabeen, K et al. (2016) in Pakistan, Induction deaths accounted for 19.2%, most of which were infection-related.[6] In Egypt, in a study by Abdelmabood S et al. (2020), induction deaths were 23%, the majority related to infections.[3] One factor for the decrease in deaths in our cohort is likely due to dropping doxorubicin from the induction regimen when L-asparaginase was more available. Using a less intensive three-drug induction regimen (prednisone, asparaginase, vincristine) has been associated with decreased early mortality (toxic deaths) and improved short-term survival compared to a more intensive anthracycline-containing induction regimen.[20,21] The other factor includes prompt recognition of neutropenic fever and initiation of empiric antibiotics. The use of antimicrobial prophylaxis has been shown to reduce significantly induction deaths related to infections.[22] In our setting, we have used cotrimoxazole, fluconazole, and ciprofloxacin prophylaxis during severe neutropenia ($<0.5 \times 10^9$/L). Invasive infections are a common complication and cause of death during induction, requiring more effective infection prevention strategies.[23] Improved supply of blood products, especially platelets, has also contributed to the supportive care of the patients during induction. At MTRH, there is an urgent need to create more space to allow for better isolation, develop antibiotic therapy guidelines based on local antimicrobial sensitivity patterns, and improve supplies of blood products to reduce induction deaths further.

Delay in diagnosis and initiation of treatment is also among the reasons for poor outcomes in LMICs.[24] Although the duration of illness did not significantly influence the outcome in the two periods, more than half of the patients had had symptoms for more than 1-month before presentation at MTRH. In India, prolonged symptom-to-diagnosis interval in childhood acute ALL adversely impacted survival, with those less than eight weeks having a better median survival of 59 +/- 5 months.[25] Dai Q et al. (2022) found that diagnosis delay was an independent predictor for treatment outcomes in childhood ALL.[26] Longer time interval to the diagnosis of ALL has been associated with more extensive disease, increased toxicity from chemotherapy, and death. Almost all the patients diagnosed at MTRH are referred from lower-level County health facilities, with no adequate expertise and diagnostic capacity, resulting in a delay in referral, diagnosis,

and initiation of treatment.

Like in the earlier cohort, further analysis of event-free survival estimates of those with NHIF at diagnosis and those without did not reveal any statistically significant difference. This could be attributed to the fact that 40 out of the 43 who did not have health insurance were assisted to be enrolled through the social work services department during the first weeks of therapy. Moreover, there is a possibility of waiver for the poorest.

Being a retrospective study, the limitations experienced included missing medical records and lack of documentation of information in some of the retrieved records.

In conclusion, there was an improvement in event-free survival and a reduction in treatment abandonment and relapse. However, induction deaths did not reduce significantly. Although the survival outcomes are much lower compared to HIC, this study highlights the importance of collaboration with institutions in HIC and LMIC.[27] and continuous quality improvement strategies that are adapted to available resources. Future strategies to reduce induction mortality should include working in collaboration with county lower-level facilities to improve early recognition, referral, diagnosis, and initiation of ALL treatment. Improved availability of blood products, especially platelets, adequate ward space for isolation, and other infection prevention strategies, including handwashing and prophylactic antimicrobial use, need to be implemented. There is a need for advocacy for universal health care through NHIF coverage and improved parental education and counseling to reduce treatment abandonment further. Proper risk stratification, use of risk-adapted protocols, and treatment of relapsed disease in resource-limited settings such as MTRH need to be studied. Collaboration with institutions in HIC through the existing twinning programs needs to be enhanced for knowledge and skills transfer. Implementing all or most of this will help us to achieve a 60% cure of patients with ALL by 2030, as stated by the WHO Global initiative on Childhood Cancer.[1]

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CONFLICT OF INTEREST

All authors declare no conflict of interest.

ETHICS APPROVAL

This study was approved by the Institutional Research and Ethics Committee of Moi University/Moi Teaching and Referral Hospital.

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27. Rivera GK, & Ribeiro RC. Improving treatment of children with acute lymphoblastic leukemia in developing countries through technology sharing, collaboration, and partnerships. *Expert Review of Hematology* 2014;7(5):649-657.**FIGURE LEGENDS**Figure 1. Comparison of survival of children through the induction phase of therapy between the two cohorts before (n=136) and after (n=123) Figure 2. Comparison of treatment abandonment between the two cohorts before (n=136) and after (n=123) Figure 3: (A) Comparisons of event-free survival of children with low WBC (<50 x 109/L) to those with high WBC (>50 x 109/L), (B) comparison of event-free survival by age group. Figure 4: (A) comparisons of event-free survival estimates before (n=136) and after (n=123) (B) overall-survival estimates for the 2017-2020 cohort (n=123)

TABLE 1 Socio-demographic and clinical characteristics of patients for the two periods

	Categories	2010-2016 (n=136)	2017-2020 (n=
Age at diagnosis (years)	Mean (SD)	7.9(4)	6.9 (4.2)
	Median (IQR)	7.8(4.5-11.2)	6 (3, 10)
Sex	Male	73(54%)	91 (57%)
	Female	63(46%)	69 (43%)
Distance to MTRH		(n=136)	(n=157)
	<100 Km	54(40%)	32 (20%)
	>100 Km	82(60%)	125 (80%)
Duration of symptoms before admission at MTRH		(N=132)	(N=156)
	<1 month	31(23%)	57 (36%)
	1-3 months	68(52%)	72 (45%)
	> 3months	33(25%)	27 (17%)
Health insurance (NHIF) status		(n=136)	(n=123)
	NHIF at the start of treatment	71(52%)	80 (65%)
	NHIF during treatment	43(32%	40 (33%)
	No NHIF	22(16%)	3 (2%)
WBC count at diagnosis (x10^9 /L) (n=123)	<50		81 (66%)
	[?]50		42 (34%)
ALL immunophenotypes (n=123)	B-cell precursor		33 (27%)
	T-cell		8 (6%)
	Not determined		82 (67%)
CNS status (n=123)	Negative		94 (76%)
	Positive		24 (20%)
	Not determined		5 (4%)

TABLE 2 Treatment outcome comparing the two cohorts before (n=136) and after (n=123)

		2010-2016 cohort (n=136)	2017-2020 cohort (n=123	p-value
First treatment outcome	Death	40(30%)	31(25%)	NS
	Relapse/progressive	35(26%)	19(16%)	0.04136
	Abandonment	33(24%)	17(14%)	0.03318
	Event free	27(20%)	56(46%)	0.00001

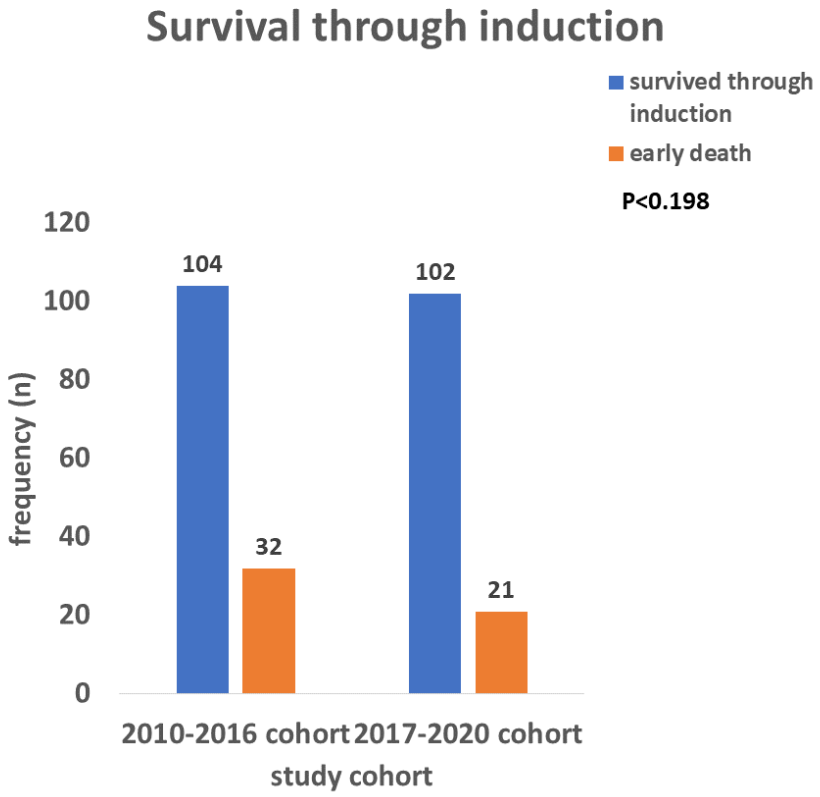


Figure 1 Comparison of survival of children through the induction phase of therapy between the two cohorts before (n=136) and after (n=123).

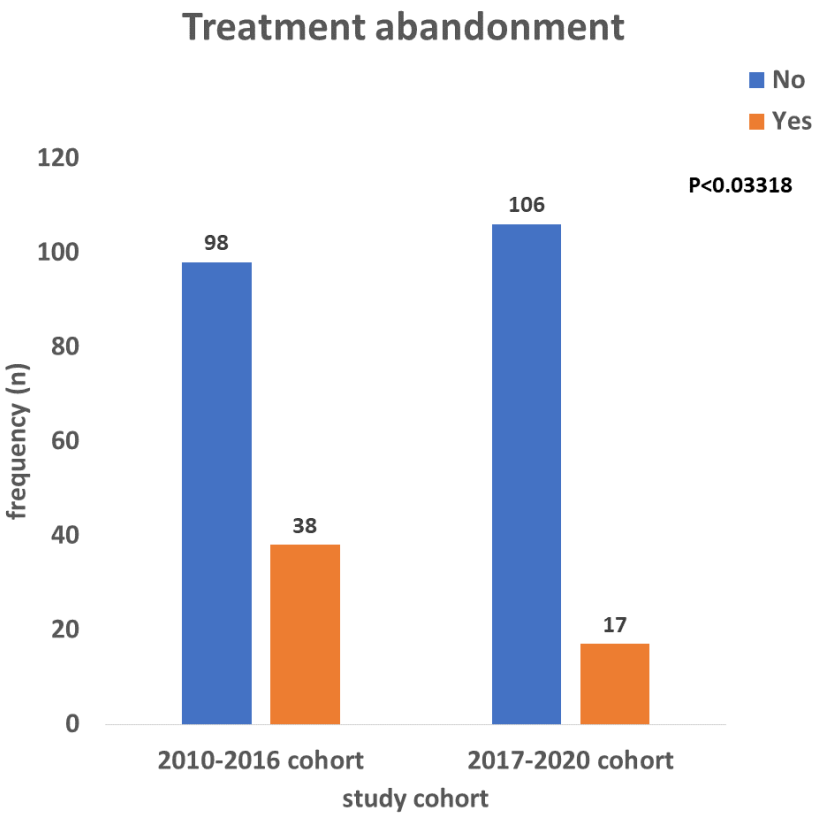


Figure 2 Comparison of treatment abandonment between the two cohorts before (n=136) and after (n=123).

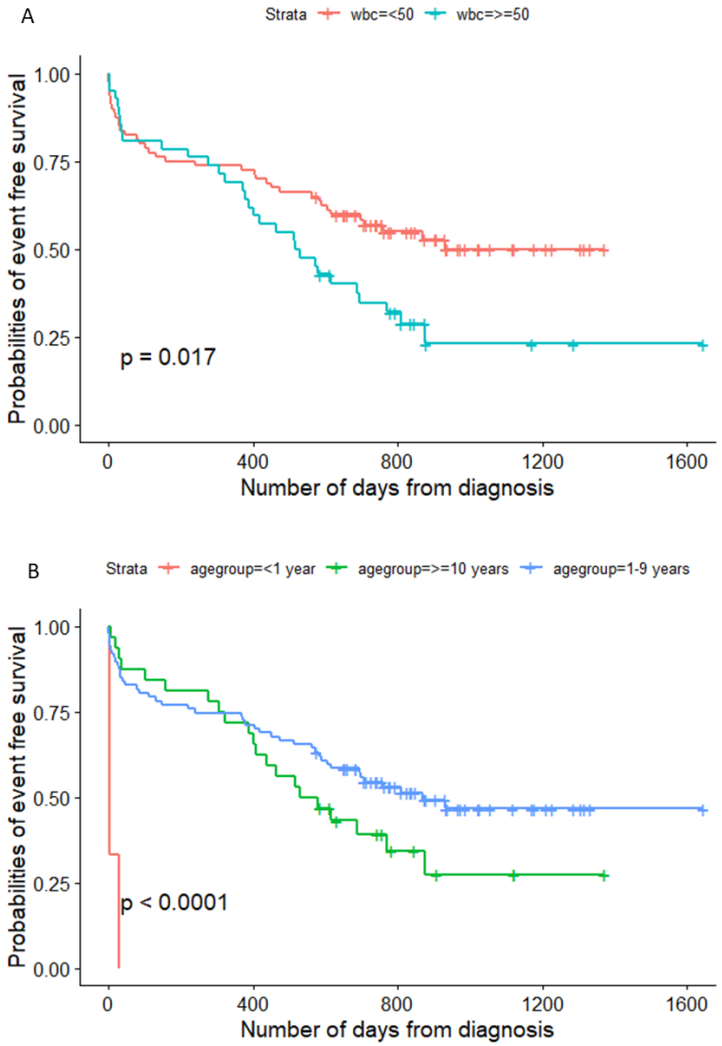


Figure 3: (A) Comparisons of event-free survival of children with low WBC (<50 x 10^9/L) to those with high WBC (>50 x 10^9/L), (B) comparison of event-free survival by age group.

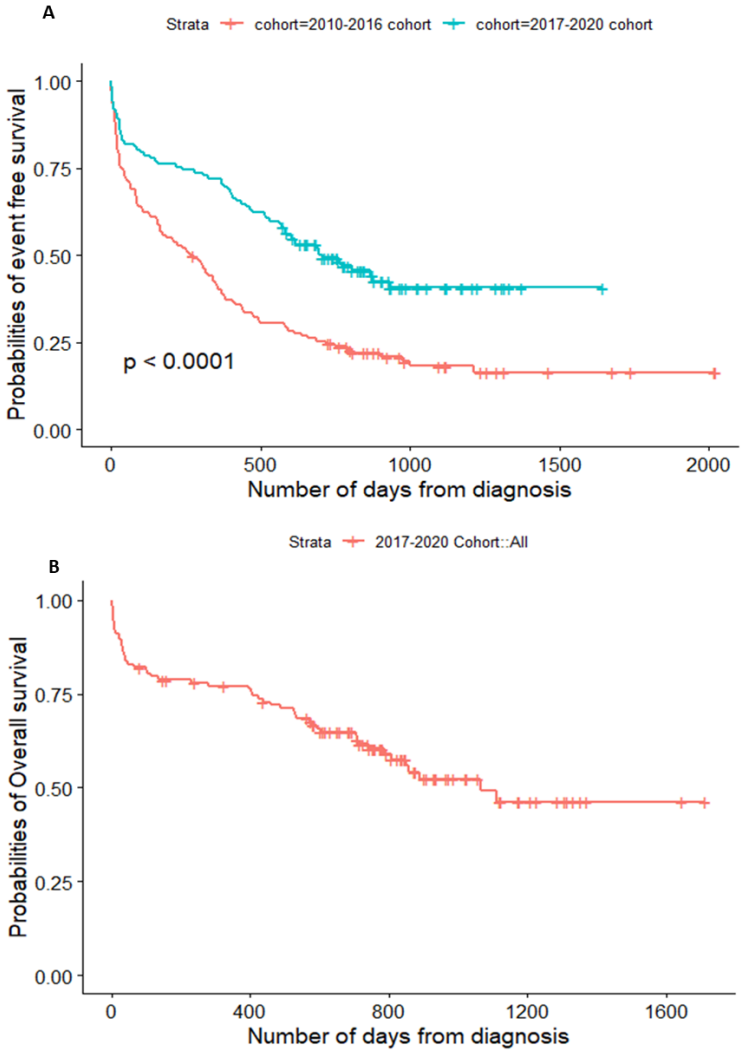
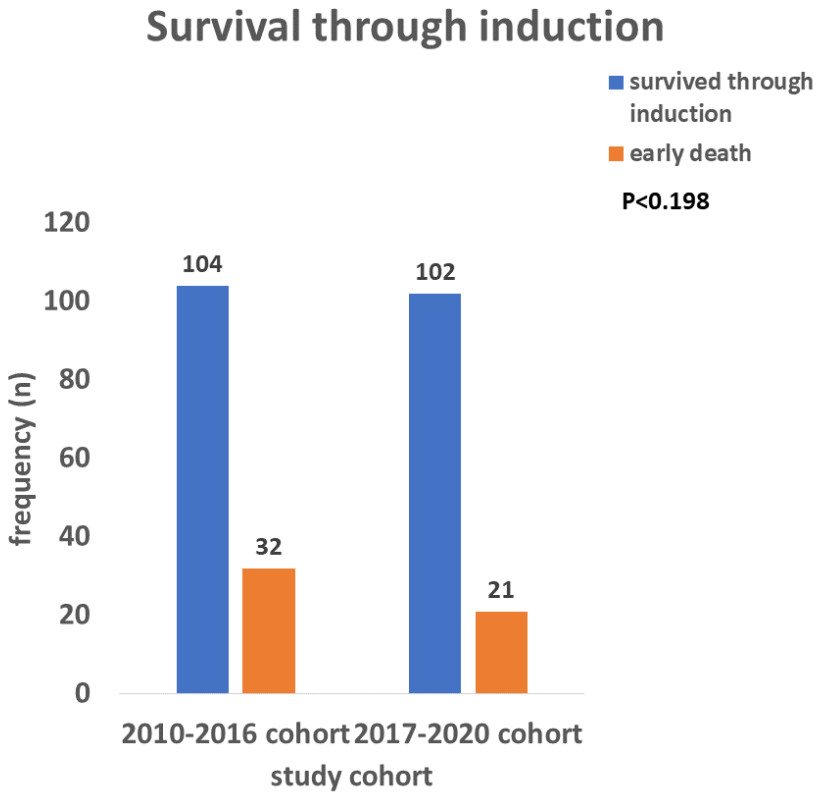
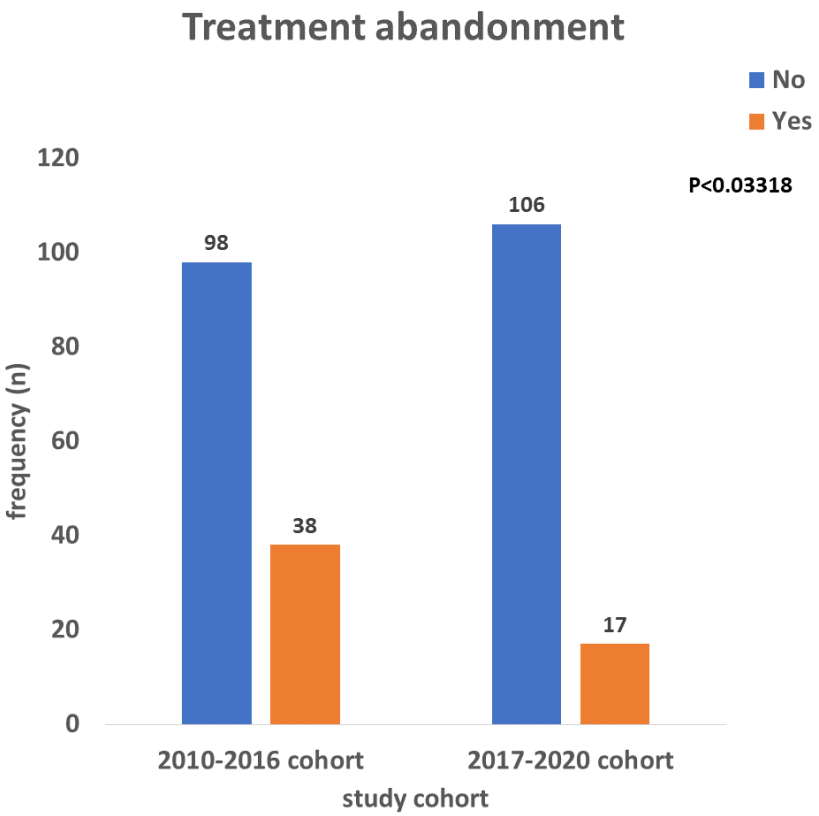
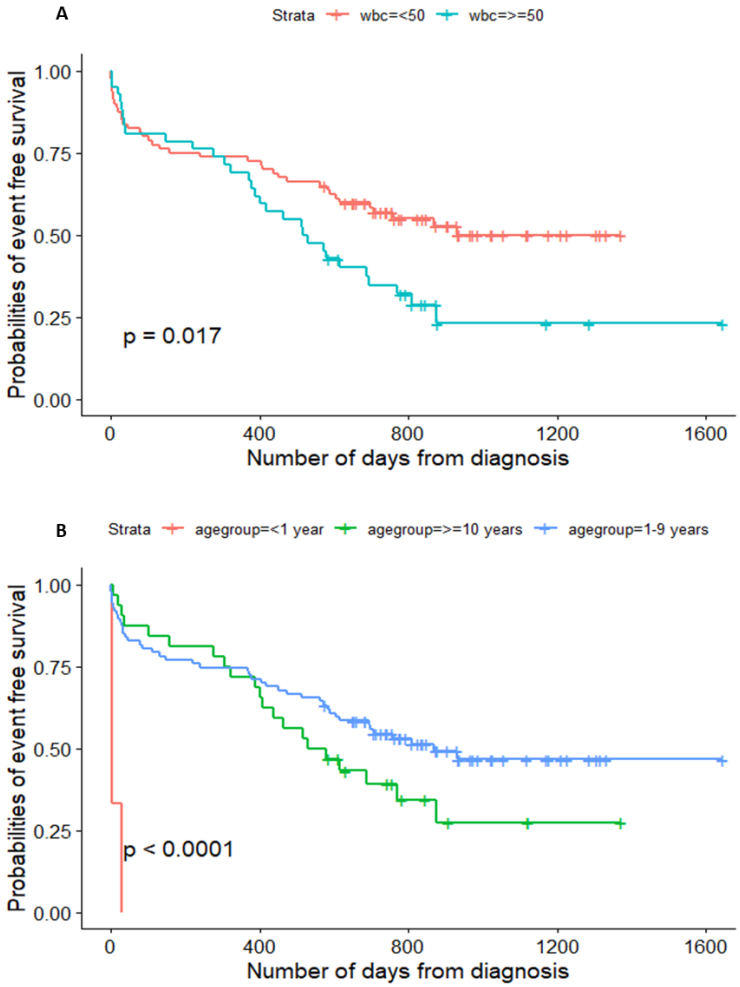


Figure 4: (A) comparisons of event-free survival estimates before (n=136) and after (n=123) (B) overall-survival estimates for the 2017-2020 cohort (n=123)







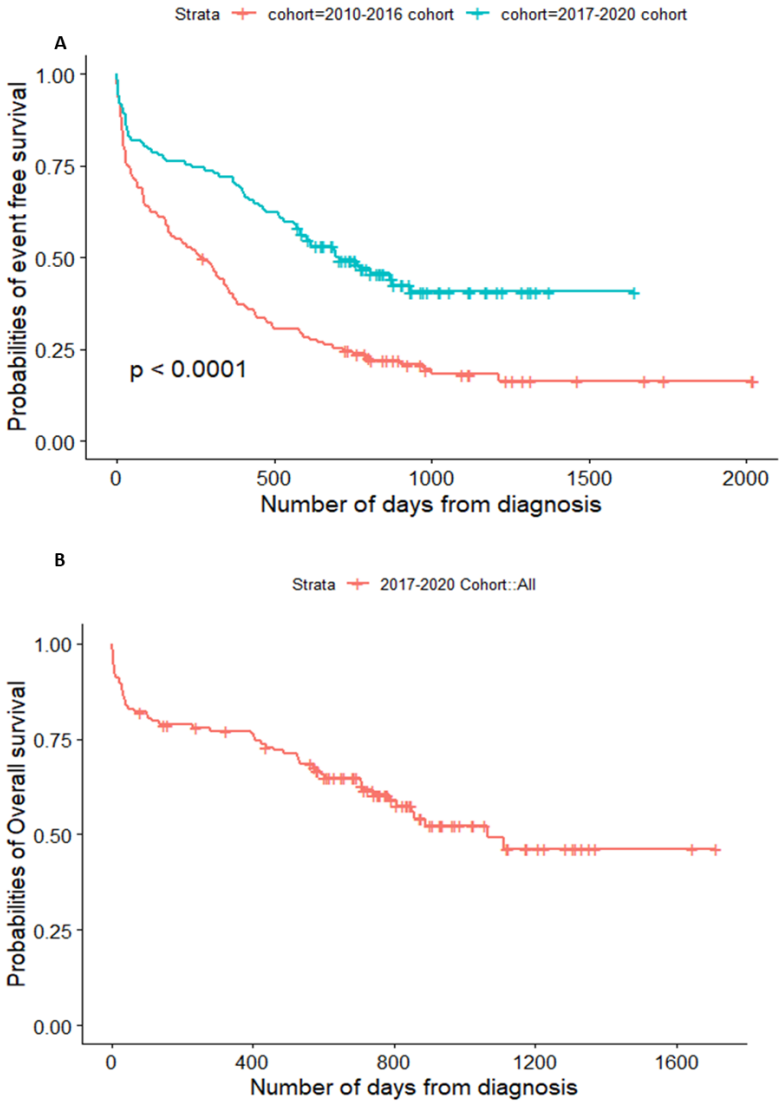


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TABLE 1 Sociodemographic and clinical characteristics.docx available at https://authorea.com/users/589671/articles/626394-improved-survival-for-childhood-acute-lymphoblastic-leukemia-in-a-low-middle-income-country-reduction-in-abandonment-and-relapse

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TABLE 2 Treatment outcomes.docx available at https://authorea.com/users/589671/articles/626394-improved-survival-for-childhood-acute-lymphoblastic-leukemia-in-a-low-middle-income-country-reduction-in-abandonment-and-relapse