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Childhood Acute Lymphoblastic Leukemia Survival in Western Kenya: Reduction in Early Deaths and Treatment Abandonment

Gilbert Olbara[1] | George Bogonko[2] | Festus Njuguna[2] | Sandra Langat[3] | Martha Kipngetich[3] | Dennis Njenga[3] | Gertjan Johannes Kaspers[4,5] | Terry Allen Vik[6]

[1]Directorate of Child Health and Pediatrics, Moi Teaching and Referral Hospital, Eldoret, Kenya | [2]Department of Child Health and Pediatrics, Moi University, Eldoret, Kenya | [3]AMPATH Oncology, Moi Teaching and Referral Hospital, Eldoret, Kenya | [4]Princess Máxima Center For Pediatric Oncology, Utrecht, the Netherlands | [5]Emma Children's Hospital, Amsterdam UMC, Vrije Universiteit Amsterdam, Pediatric Oncology, Amsterdam, the Netherlands | [6]Department of Pediatrics, Division of Hematology-Oncology, Indiana University School of Medicine, Indianapolis, Indiana, USA

Correspondence: Gilbert Olbara (olbara112@yahoo.com)

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ABSTRACT

Background: An earlier study on children diagnosed with acute lymphoblastic leukemia (ALL) at Moi Teaching and Referral Hospital (MTRH) in Kenya reported a low event-free survival (EFS), excess treatment abandonment, and high induction mortality. Based on these observations, our team focused on implementing strategies to reduce the causes of poor outcomes.

Intervention: The interventions were designed to reduce toxic deaths while maintaining the efficacy of treatment. The strategies included are as follows: (1) substituting asparaginase for doxorubicin in induction; (2) enhanced supportive care, increased access of antibiotics and blood products; (3) enhanced social and financial support for all underserved patients at the time of diagnosis. Our study compared childhood outcomes of ALL treatment before and after implementation of these intervention strategies at MTRH.

Methods: We retrospectively reviewed the medical charts of 123 children diagnosed with ALL between 2017 and 2020 (*cohort 2*). Their clinical profiles and treatment data were collected and subsequently compared to that of 136 children diagnosed between 2010 and 2016 (*cohort 1*) before the implementation of the interventions above. Survival analysis was compared using the Kaplan–Meier method.

Results: Three-year EFS estimates improved from 18% to 41% ($p = 0.0001$). Relapse and progressive disease decreased from 26% to 16% ($p = 0.04136$), and the abandonment decreased from 24% to 14% ($p = 0.03318$), respectively. Deaths in induction decreased from 24% to 17% ($p = 0.198$). Children between 1 and 9 years and those with white blood cell (WBC) count $<50 \times 10^9$/L had better EFS (50% vs. 26%, $p < 0.001$ and 50% vs. 24%, $p = 0.017$, respectively).

Conclusions: Use of systematically generated data and application of locally adapted interventions led to a reduction in treatment failure and increased survival. Improved access to asparaginase by working with local suppliers and increased insurance coverage through parental education and philanthropies are strategies that could be adopted by centers in low- and middle-income countries. More efforts are required to improve risk stratification for newly diagnosed ALL patients.

ALL, acute lymphoblastic leukemia; EFS, event-free survival; HIC, high-income country; LMIC, low-middle-income country; MTRH, Moi Teaching and Referral Hospital; NHIF, National Hospital Insurance Fund; OS, overall survival.

1 | Introduction

ALL is the commonest childhood malignancy, accounting for 30% of cancers diagnosed in this age group. While survival in high-income countries (HIC) exceeds 90% [1–4], in low- and middle-income countries (LMICs), the survival is often less than 35% [5–8]. This survival inequity has been attributed to several systemic factors unique to LMIC including late presentation, delayed diagnoses, treatment abandonment, and treatment-related deaths [5, 6, 9–11]. In LMIC, these factors result in ineffective ALL treatment, disease progression, and excess deaths during treatment [7, 12–14].

In our previous study conducted in western Kenya [7], we identified early induction deaths as the primary cause of treatment failure in children diagnosed with ALL. These deaths were often attributable to treatment-related toxicity, particularly among patients who were severely ill at the time of diagnosis. Similar findings have been reported in other African studies, underscoring that inferior outcomes in childhood ALL are frequently driven by factors external to the disease itself [12, 14, 15].

Socioeconomic challenges including high cost of treatment and limitations in healthcare infrastructure play a significant role [9–11]. Late presentation for diagnosis, poor adherence to treatment—often due to financial constraints, long travel distances to treatment centers, and low literacy levels within families—complicate the delivery and effectiveness of care. Furthermore, the presence of comorbid conditions including malnutrition and deaths related to treatment contribute to the high rates of early mortality observed in these settings [12, 14, 16]. We therefore implemented strategies that were expected to improve survival by addressing local challenges to the treatment of ALL in our setting. Since 2010, our team has systematically collected clinical and treatment data of all patients diagnosed at the treatment center in a simple Excel registry and used the analyzed data to inform quality improvement decisions and treatment pathways [10]. This study aims to evaluate the impact of interventions implemented during *cohort 2* (2017–2020) at Moi Teaching and Referral Hospital (MTRH) and compare the survival outcomes pre- and post-intervention period.

2 | Methods

2.1 | Setting

According to the World Bank data, Kenya is an LMIC with an estimated population of 55 million with children accounting for 40% as of the year 2021. The population below the poverty line was estimated at 39.8% as of 2022 [17]. Over 70% of the Kenyan population did not have National Health Insurance (NHIF) coverage. Those without any insurance pay hospital bills out of pocket [21].

The study was conducted at MTRH, the country's second-largest public hospital offering comprehensive pediatric cancer treatment. It serves a catchment population of about 25 million people in western Kenya. On average, 240 children were diagnosed with cancer annually during the study period. The pediatric oncology unit has a capacity of 35 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 of local experts in collaboration with visiting pediatric hematology-oncologists from our partner institutions in the Netherlands and the USA. The visiting experts spend approximately 10 weeks annually supporting care of children. They have played key roles in helping the development, adaptation, and revision of the treatment protocols over time. The collaborating experts also engage in educational activities for all cadres of health care providers, research, and fundraising to support the patients. A key highlight is the annual pediatric workshop now in its 16th year, targeting the sensitization of primary health care providers and pediatricians from the MTRH catchment area.

2.2 | Intervention

Three primary interventions occurred during *cohort 2* (between 2017 and 2021) of treatment. The interventions were designed through collaborative efforts by teams at MTRH, Indiana University through the AMPATH (Academic Model providing Access to Care) Consortium, and twinning partners the Princess Maxima Center of Paediatric Oncology in the Netherlands. To reduce toxicity observed in *cohort 1*, the induction regimen was modified to reduce myelosuppression by excluding doxorubicin. Patients in cohort 2 received a three-drug induction (vincristine, prednisone, and L-asparaginase) for 6 weeks (Table 1).

The second intervention focused on strategies to improve supportive care. One strategy was implementing continuous training and sensitization activities within the oncology unit and laboratory to educate the multidisciplinary care team on the urgency of neutropenic fevers and need for infectious prophylaxis in the immunocompromised patients. There was also emphasis on improving access to antimicrobials by engaging the pharmacy department through our clinical pharmacist who was part of the care team. To improve access to blood products, the care team worked with both the hospital management and blood bank leadership to prioritize the pediatric oncology unit. Despite significant and frequent blood shortages within the hospital, the nursing team was able to proactively communicate with blood bank teams and get reasonable supplies of either packed red cells or platelets for the critical patients.

The third intervention was financial protection for the families. This started with a social worker encounter for all newly diagnosed children with cancer at the time of diagnosis. All those without a health insurance (NHIF) at the time of the diagnosis were identified and supported by dedicated patient navigators to enroll for NHIF. Funding was made available through two philanthropic organizations, which paid NHIF fees amounting to 60 USD per child equivalent to one year of NHIF subscription for the most vulnerable families. This covered any hospital inpatient health care costs for the child in any Kenyan public facility for a whole year. All parents were encouraged to participate in a weekly parental education program and biweekly parental support groups focusing on education about childhood cancer and the importance of treatment adherence.

TABLE 1 | Components of the ALL-treatment regimens comparing cohort 1 (2010–2016) and cohort 2 (2017–2020).

Treatment description	Cohort 1	Cohort 2
Time period	2010–2016	2017–2020
Total treatment duration (weeks)	104	102
Induction duration (weeks)	6	6
Induction drugs	4	3
Adriamycin in induction (25 mg/m^2)	2 doses (Weeks 2 and 3)	None
L asparaginase (6000i.U/m^2)	3 doses	15 doses
Delayed intensification adriamycin (25 mg/m^2)	1 dose; Week 16	2 doses; Weeks 18 and 19
Methotrexate 1500 (mg/m^2)	Weeks 9, 11, and 13	Weeks 9, 11, 13, and 15

2.3 | Study Design

This was a retrospective study of children (0–16 years) diagnosed with ALL at MTRH from January 2017 to December 2020. We included all children diagnosed with ALL, regardless of their clinical condition, even if they died of the disease before starting treatment. Previous medical record data from *cohort 1* (2010–2016) were available for comparison.

The diagnosis of ALL was made based on a bone marrow examination by the pathologists showing more than 25% blasts on the bone marrow aspirate. Flow cytometry confirmed the diagnosis in some cases, although this was not available to all patients during the study period due to financial constraints. Cytogenetics was not available at the time of the study.

The children with ALL at MTRH were treated with a modification of the Dutch Oncology Group ALL-6 Study protocol therapy for non-high-risk ALL [18]. All patients received the same standard treatment without risk stratification and consisted of 3-drug induction (6 weeks), consolidation (2 weeks), methotrexate phase (7 weeks), re-induction (3 weeks), and maintenance therapy (83 weeks). The additional modification during *cohort 2* period included intensified L-asparaginase therapy and a fourth high-dose methotrexate. The duration of ALL treatment lasted for 104 weeks (Tables S1and S2).

For each patient, sociodemographic data were collected, including age, gender, the distance of residence from MTRH, and duration of symptoms. In addition, we obtained data on health insurance status and treatment outcomes from the medical records. We defined events as abandonment, death, relapsed or progressive disease, or event-free survival (EFS). EFS was based on the time from diagnosis to the date of the first treatment outcome (death, relapse/progressive disease, abandonment, or alive at the 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.

Additional clinical data for *cohort 2* included white blood cell (WBC) count at diagnosis, ALL immunophenotype, and central nervous system (CNS) disease status, although these data were not available for *cohort 1* for comparison. We determined survival through induction, and the survival estimates by WBC, sex, age at diagnosis, health insurance status (NHIF) at diagnosis, EFS, and OS.

Refusal to start or continue with planned treatment for four or more consecutive weeks was considered treatment abandonment [16]. Induction mortality was defined as deaths that occurred before the start of treatment [12] or during induction (< 42 days from the start of treatment). 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 or the presence of clinical symptoms and signs suggestive of CNS involvement including cranial nerve palsies and focal brain dysfunction.

Ethical approval for this study was obtained from the MTRH and Moi University Institutional Review Board/Ethics Committee Approval No. FAN IREC 3023. All participants provided written/verbal informed consent prior to participating in the study. The study was conducted in accordance with the ethical standards of the Declaration of Helsinki. The study was not registered as a clinical trial. No written consent for publication has been obtained from the patients as there is no patient-identifiable data included in this manuscript.

2.4 | 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 and Fisher's exact tests, where applicable. The level of significance was set for a p value < 0.05. Survival estimates were determined using the Kaplan–Meier method and notated as pEFS and pOS.

The primary outcomes were EFS and OS while the secondary outcomes were survival estimates by WBC, age at diagnosis,

TABLE 2 | Sociodemographic and clinical characteristics of patients in cohort 1 (2010–2016) and cohort 2 (2017–2020).

	Categories	2010–2016	2017–2020	*p* value
Age at diagnosis (years)		$N = 136$	$N = 160$	
	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%)	0.581142
	Female	63(46%)	69 (43%)	
Distance to MTRH		$N = 136$	$N = 157$	
	< 100 km	54(40%)	32 (20%)	0.000292
	> 100 km	82(60%)	125 (80%)	
Duration of symptoms before admission at MTRH		$N = 132$	$N = 156$	
	< 1 month	31(23%)	57 (36%)	0.039938
	1–3 months	68(52%)	72 (45%)	
	> 3months	33(25%)	27 (17%)	
Health insurance (NHIF) status		$N = 136$	$N = 123$	
	NHIF at diagnosis	71(52%)	80 (65%)	0.000721
	NHIF during treatment	43(32%	40 (33%)	
	No NHIF	22(16%)	3 (2%)	
WBC, immunophenotype, and CNS status 2017–2020			$N = 123$	
WBC count at diagnosis	$<50 \times 10^9$ /L		81 (66%)	
	$\geq 50 \times 10^9$ /L		42 (34%)	
ALL immunophenotypes	B-cell precursor		33 (27%)	
	T-cell		8 (6%)	
	Not determined		82 (67%)	
CNS status	Negative		94 (76%)	
	Positive		24 (20%)	
	Not determined		5 (4%)	

and health insurance status (NHIF) at diagnosis. The analysis of prognostic factors was based on the EFS and the comparison of curves by the log-rank test.

3 | Results

The sociodemographic and clinical characteristics of the two cohorts are represented in Table 2. There was no difference in age and sex distribution between cohort 1 ($n = 136$) and cohort 2 ($n = 160$). Of note, the number of patients with no health insurance at diagnosis decreased from 16% in cohort 1 to 2% in cohort 2. The number of deaths did not change significantly during both cohorts. Deaths in induction decreased from 32 (24%) to 21(17%) ($p = 0.198$), constituting 80% and 68% of the deaths, respectively, that occurred during treatment. Out of these, six were attributed to infectious causes, five were disease related, while the remainder were not classified. Abandonment decreased from 24% to 14% between the two cohorts ($p = 0.033$). Most cases of treatment abandonment occurred during maintenance therapy: 18 out of 33 (54.5%) in 2010–2016 and 15 out of 17 (88.2%) in the 2017–2020 period. Relapse/progressive disease decreased significantly ($p < 0.041$), with most relapses occurring during maintenance in both cohorts: 70% for cohort 1 and 67% for cohort 2. The mean time to relapse was 466.5 days. Patients who died in induction decreased from 24% to 17% between the two cohorts ($p = 0.20$). Table 3 shows treatment outcomes for participants in cohort 1 and cohort 2.

Figure 1A shows EFS curves for the two cohorts. The pEFS at 3 years significantly improved from 18% (95% CI, 0.123–0.268) to 41 % (95% CI, 0.319–0.518) ($p < 0.0001$). Figure 1B shows the OS curves for cohort 2 alone (no data for cohort 1) with a 3-year pOS of 49.2% (95% CI, 39.1% to 62%).

In *cohort 2*, 24 children (20%) had CNS disease and received three intrathecal (cytarabine, methotrexate, and hydrocortisone) chemotherapy (Table S1). Among these patients, four (17%) were referred for craniospinal radiation (there were no radiotherapy services at MTRH at that time). Thirteen patients (54%) died dur-

TABLE 3 | Treatment outcome comparing cohort 1 ($n = 136$) and cohort 2 ($n = 123$).

		cohort 1 ($n = 136$)	cohort 2 ($n = 123$)	p value
First treatment outcome	Death	40(30%)	31(25%)	Not significant
	Relapse/progressive	35(26%)	19(16%)	0.04136
	Abandonment	33(24%)	17(14%)	0.03318
	Event free	27(20%)	56(46%)	0.00001

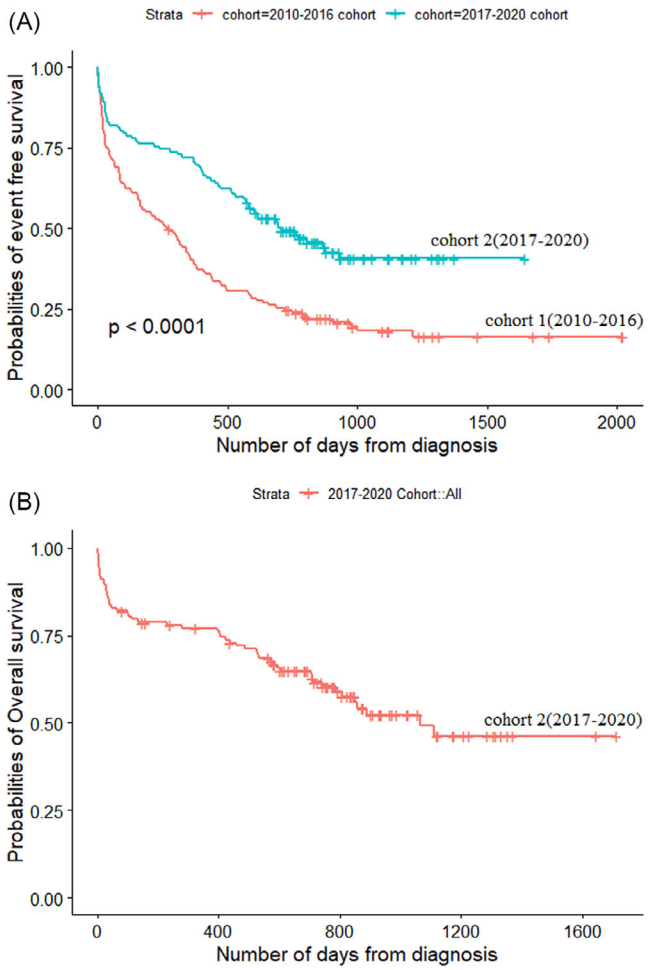

FIGURE 1 | (A) Comparisons of event-free survival curves in cohort 1 ($n = 136$) and cohort 2 ($n = 123$). (B) Overall-survival curve for cohort 2 ($n = 123$).

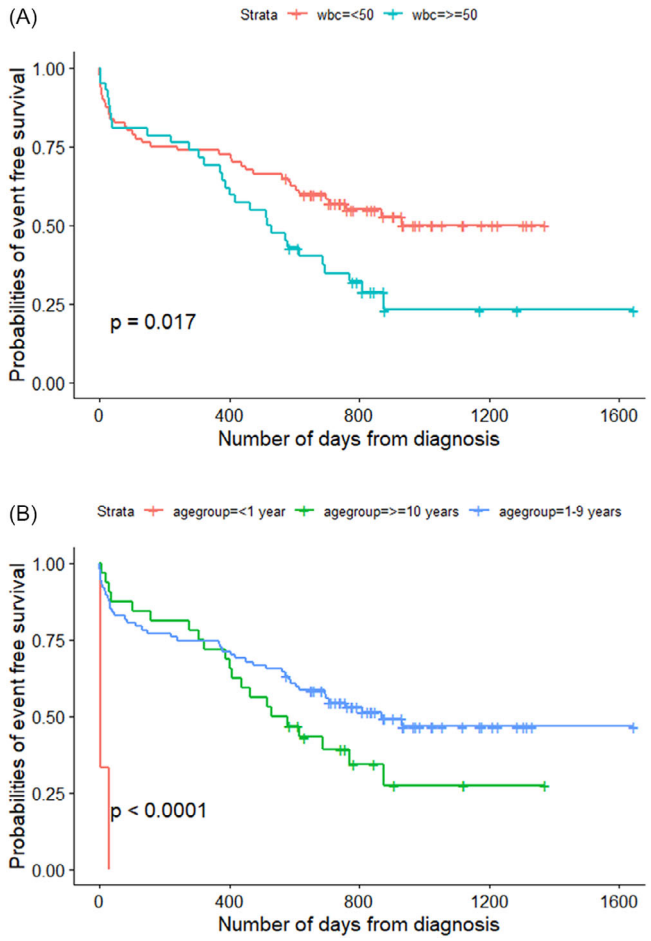

FIGURE 2 | (A) Comparisons of event-free survival of children with low WBC ($< 50 \times 10^9$/L) to those with high WBC ($> 50 \times 10^9$/L). (B) Comparison of event-free survival by age group.

ing treatment, and four (13%) were among those who abandoned treatment. Seven (17%) were still alive, of whom 3 are among those who received craniospinal radiotherapy in addition to intrathecal chemotherapy.

Age and WBC count at diagnosis significantly influenced EFS in cohort 2. Figure 2A shows EFS by WBC count at diagnosis. Patients with WBC count $<50 \times 10^9$/L had better EFS compared to those with $>50 \times 10^9$/L ($p < 0.017$). Figure 2B shows that children between the age of 1 year and 9 years had better EFS, while those below 1 year of age had the worst outcome ($p < 0.0001$).

4 | Discussion

This study evaluates treatment outcomes of two cohorts of pediatric patients diagnosed with ALL in an LMIC over a decade. The goal was to compare the impact of interventions aimed at reducing early deaths and treatment abandonment between *cohort 1* (2010–2016) before interventions and *cohort 2* (2017–2021) after protocol changes in 2017. Interventions implemented included omitting doxorubicin, consistently using *Escherichia coli* L-asparaginase during induction treatment and enhancing use of prophylactic and empiric antibiotics during neutropenic episodes. In addition, newly diagnosed uninsured patients were enrolled into a national health insurance scheme with sup-

port from philanthropic organizations. These interventions were guided by findings from an earlier study that reported excess induction mortality and treatment abandonment [7]. Our results show a decline in induction deaths (26% vs. 16%), treatment abandonment (24 % vs. 14%), and relapsed disease (26% vs. 16%) ($p = 0.04136$), leading to improved 3-year pEFS (41% vs. 18%) ($p = 0.0001$) between *cohort 2* and *cohort 1*, respectively.

Studies in LMIC have reported similar observations with early deaths in induction, treatment noncompliance, and relapses as main causes of poor survival outcomes in resource-constrained countries ranging from 20% to 40% [12, 14, 15]. Moreover, attempts to intensify treatment regimens in LMIC or implement protocols from HIC in the context of inadequate supportive care infrastructure do not necessarily translate into improvements in survival [19, 20]. While ALL remains a highly curable in HIC [1, 2], the biggest challenge for clinical teams in LMIC is in designing an approach that optimizes available treatment regimens to address local challenges.

In our study, early deaths in *cohort 2* declined from 26% to 16% compared to the historical cohort. Refinement in classification as to whether these were from infectious etiology or disease related was not available due to the retrospective nature of this study. Some studies in LMIC have made better efforts in defining early deaths. For instance, Jabeen et al. in Pakistan reported induction deaths of 19.2%, mostly infection-related [9, 21], while a study in Egypt found 23% of overall mortality during induction was due to infections [24]. In contrast, early deaths in HIC studies rarely exceed 5% due to the optimal supportive care infrastructure and standardized care guidelines [2, 22].

Patient factors such as patient age, type of treatment, the presence of comorbid conditions, and high leucocyte counts at diagnosis have consistently been identified as predictors of early mortality in ALL patients [18, 23]. The decline in early deaths in the post-implementation cohort is likely due to the omission of doxorubicin in the initial weeks of treatment. Anthracyclines are often associated with prolonged myelosuppression [19, 24, 25]. Most children are severely ill, undernourished, and immunocompromised at diagnosis. Therefore, using a less intensive 3-drug induction regimen (prednisone, asparaginase, and vincristine) was a more pragmatic approach for our patients. Such regimens with de-escalated anthracycline intensity have been associated with reduced induction mortality and improved short-term survival [19, 26]. Several study groups have shown the feasibility of reducing intensity by sensibly adapting treatment to local context, either by reducing dosage or omitting certain classes of chemotherapy [19, 20, 25].

Other contributors to improvement in survival were the prompt recognition of neutropenic fevers and judicious use of both prophylactic and empiric antibiotics. Use of sulfamethoxazole-trimethoprim prophylaxis throughout the treatment course and azoles during periods of persistent neutropenia significantly reduces deaths related to infections [13, 27]. During both study periods, there were no dedicated isolation rooms for the profoundly neutropenic patients. The team, however, focused efforts on prompt diagnosis and early initiation of antibiotics as a strategy. Clinical teams were continually sensitized and trained to promptly identify neutropenic patients and initiate empiric therapy in those with fevers based on a standard local guideline available within the wards. Availability of antibiotics was guaranteed by working with the clinical pharmacy team and hospital pharmacy, ensuring minimal stock outs of selected antibiotics. Fortunately, all drugs available within the hospital formulary were fully paid for by the NHIF if the patient was admitted at our hospital. Improved multidisciplinary communication with ancillary teams enhanced the supply of blood and blood products despite shortage within the hospital. Further efforts to design and document infection prevention guidelines and designate isolation spaces may be warranted to further sustain these improvements [21, 27, 28].

Treatment abandonment remains a significant cause of treatment failure, with rates ranging from 7.5% to 35% in more recent LMIC studies [6, 12, 29]. This has been attributed to the economic situations of parents and geographic limitations hindering access to cancer care in LMIC [11, 29, 30]. In addition, the absence of medical insurance and financial toxicity related to treatment increases the risk of non-compliance by parents [10, 29]. In our study, treatment abandonment significantly declined from 24% to 14% in *cohort 2* because of implementing a cost-effective psychosocial measure. The main intervention involved pretreatment screening by the social worker and enrolling uninsured parents, particularly those who couldn't afford the $60 USD annual cost at the time of diagnosis. These efforts, combined with regular parental education and supportive care program initiated around the same time helped retain and educate newly diagnosed parents on the importance of adhering to treatment protocols. We hypothesize that the higher rate of treatment abandonment during the maintenance phase is primarily driven by increased financial burdens associated with monthly travel to the treatment center for follow-up visits and medication refills. In many cases, insurance coverage had been exhausted by this stage of therapy, resulting in greater out-of-pocket expenses for families. In most studies, risk factors for treatment abandonment have been effectively identified and associated to low EFS in LMIC [29, 30]. Interventions in LMIC should therefore be focused addressing both the financial and psychoeducational contributors to treatment abandonment, resulting in universal access to care and better comprehension of cancer and its treatment. Initially, this will demand strong collaborative efforts supported by partners and philanthropists, but ultimately governments in LMIC will need to implement policies targeted at universal care and financial protection for childhood cancers [29, 31].

ALL relapses are a critical outcome event determining the balance between the intensity versus the toxicity and a good measure of success of treatment. In the landmark cooperative trials of the 90s on ALL treatment, concern for early relapses was a key research question [32, 33]. These studies reported that half the patients with ALL could be safely cured with low-intensity therapy [33, 34]. In our study, there was a decline in the rates of relapses from 26% to 16% in cohort 2, corroborating other recent studies [19, 26] and further proving it is possible to carefully adapt HIC treatment protocols in LMIC without necessarily increasing rates of relapses. In this study, consistent availability of *E. coli* asparaginase in the hospital and the fact that most patients were likely precursor B cell immunophenotype were possible reasons contributing to the success of treatment for cohort 2. Contrastingly, Rubagumya et al. reported 53% relapse rates using

a low-intensity regimen in Rwanda [14]. It is useful to note that participants in this study had higher mean age at diagnosis, and two-thirds had T-cell immunophenotype. These patients, with known high-risk characteristics, theoretically require more intensified treatment from the onset to minimize relapse risk [16, 35, 36]. Risk stratification and intensification of traditional chemotherapy for these high-risk cohorts improves their survival to above 70% even in LMIC [8, 35]. Therefore, targeted infrastructural investments in basic laboratory and incorporation of simple flow cytometry algorithms into routine practice will help identify those patients fit for treatment escalation while reducing toxic exposures for the low-risk curable subtypes of ALL [37, 38].

The 20% improvement reported in this is a result of the summation of reduced early deaths, reduced abandonments during therapy, and the significant reduction in relapsed or progressive disease. Whereas the causal effect cannot be fully determined by the methodology employed, this study shows it is feasible to tailor cost-effective strategies based on local data registry in improving OS of children with cancer in an LMIC setting. In our case, going forward, it would be prudent to stratify patients using available published criteria [37, 38] to identify the slow responders and the high-risk group for more intensified treatment and supportive care. An additional 50% improvement on the current findings would make our survival outcomes comparable to other established pediatric oncology units in LMICs [16, 35, 39].

There were some limitations in this study. Being retrospective, access to complete medical records was limited, and some classifications were incomplete. The absence of stratifying data in the initial cohort also hindered the comparison between the two cohorts. Nevertheless, the large pool of baseline data collected over a long period provides a reasonable example of the utility of a systematically collected data registry and its application in clinical care improvement. This also offers foundational results that can refine future studies.

In conclusion, this study shows that with strategic adaptation of treatment protocols in LMIC based on local data, reduction in induction mortality and treatment abandonment, it is possible to double survival outcomes from the baseline. More governmental commitment is required to augment efforts made by philanthropic organizations and collaborators toward expanding access to care through interventions like universal health coverage and uninterrupted access to medicines for cancer patients. Institutions should continually invest in prospective basic local registries, enhanced supportive care, and diagnostic infrastructure to characterize, stratify, and tailor treatment pathways for their patients.

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Conflicts of Interest

The authors declare no conflicts of interest.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Supporting File 1: pbc70526-sup-0001-SuppMat.pdf