Treatment outcomes and Relapse determinants in Pediatric Acute Lymphoblastic Leukemia Patients Treated at Tikur Anbesa Specialized Hospital: A Retrospective cohort Study

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Abbreviations/Synonyms

AA:	Addis Ababa
AHR:	Absolute hazard ratio
ALL:	Acute Lymphoblastic Leukemia
B-ALL:	B-cell Acute Lymphoblastic Leukemia
BLSH:	Black Lion Specialized Hospital
CAR:	Chimeric Antigen Receptor
CI:	Confidence Interval
CNS:	Central Nervous System
CSF:	Cerebrospinal Fluid
EMoH:	Ethiopian Ministry of Health
EFS:	Event-free survival
ETB:	Ethiopian birr
HICs:	High-Income Countries
HSCT:	Hematopoietic Stem Cell Transplantation
IHC:	Immunohistochemistry
IRB:	Institutional Review Board
LMICs:	Low- and Middle-Income Countries
LDH:	lactate dehydrogenase
MRD:	Minimal Residual Disease
OR:	Odds Ratio
OS:	Overall survival
RLSs:	Resource-Limited Settings
RFS:	Relapse-free survival
TLS:	Tumor lysis syndrome
TAPPCO:	Tesfa Addis Parents Childhood Cancer Organization
WBC:	White Blood Cell
WHO:	World Health Organization

Abstract

Background: Acute lymphoblastic leukemia accounts for approximately 75% of childhood leukemias worldwide. The overall survival exceeds 90% in high-income countries. The Outcome in low- and middle-income countries remains suboptimal, including Ethiopia (10–40%). Relapse is reported in 25–35% of LMIC cases and is a major contributor to mortality. Predictors of relapse in this setting remain insufficiently characterized.

Methods: A retrospective cohort study included children younger than 18 years with newly diagnosed ALL treated at Tikur Anbessa Specialized Hospital between 2020 and 2025. Overall and relapse-free survival were demonstrated with Kaplan–Meier survival analysis, predictors for death and relapse were evaluated with R using bivariate and multivariate Cox proportional hazards models at $p < 0.05$.

Results: A total of 251 children were included (male: female (1.5:1); median age 6.2 years; median follow-up 20.1 months). At diagnosis, 52.2% were standard-risk and 47.8% high-risk; nearly half were undernourished. Immunophenotyping and cytogenetic testing were infrequently performed. Infections accounted for 42 % of deaths, mainly during induction. Treatment abandonment occurred in 11.2%. OS was 74.9% at 1 year and 54.5% at 4 years. Relapse occurred in 14.4%, predominantly in the bone marrow (36.8%), with RFS of 70.5% at 1 year and 45.9% at 4 years. Relapse had a dismal outcome with an OS of 32.9 at 3 years. Infants had higher mortality (AHR 4.58 vs >10 years; AHR = 11.1 vs 1–10 years), and treatment abandonment increased mortality 2.41-fold. High WBC strongly predicted relapse: >100,000/μL (AHR = 7.47) and 50,000–100,000/μL (AHR = 3.52) compared with WBC <20,000/μL.

Conclusion: Survival and relapse outcomes in pediatric ALL patients in Ethiopia remain suboptimal, with infant age, elevated WBC, infection, and treatment abandonment driving mortality and relapse. Strengthening supportive care, early diagnosis, and diagnostic capacity is crucial for improving outcomes.

KEY WORDS: Pediatric Acute Lymphoblastic Leukemia,Relapse, Outcomes, Treatment Abandonment, Predictors for outcomes

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1. Introduction

1.1. Background of the Study

Acute lymphoblastic leukemia is the most common hematologic malignancy in children, making up about 75% of all childhood leukemia cases worldwide (1). Most pediatric ALL cases are B-cell precursor ALL, which accounts for nearly 85%, while T-cell ALL accounts for the rest (2).

The disease starts when lymphoid progenitor cells in the bone marrow become cancerous, causing them to multiply uncontrollably and crowd out normal blood cell production. This often leads to anemia, low platelets, and low neutrophil counts, which show up as fatigue, bleeding, and more frequent infections in children (3). Leukemia potentially spreads to other sites including the CNS, lymph nodes, liver, spleen, and testes. (3).

Molecularly, ALL is a heterogeneous characterized by diverse genetic and epigenetic alterations. These alterations potentially disrupt the normal lymphoid differentiation, cell cycle regulation, and apoptotic pathways. These play a leukemogenesis and influence treatment response and relapse risk. Increasing evidence indicates that specific molecular subtypes, with PAX5 altered and IKZF1 deleted leukemia, are associated with inferior outcomes and higher relapse rates (4).

Over the past several decades, the prognosis of pediatric ALL has improved dramatically in high-income countries. The implementation of risk-adapted, multi-agent chemotherapy protocols, supported by advances in supportive care and by minimal residual disease-guided treatment intensification, has resulted in long-term survival rates exceeding 90% in many settings (5)(7). Large cooperative group trials, such as those conducted by the Children's Oncology Group, have been instrumental in refining treatment strategies and optimizing outcomes through protocol modifications (7).

In contrast, children in low- and middle-income countries continue to experience substantially poorer outcomes with reported survival rates in LMICs ranging widely between 20% and 70%, reflecting marked disparities in access to timely diagnosis, advanced diagnostics, consistent chemotherapy delivery, and adequate supportive care

(6)(11). Relapse rates are correspondingly higher, frequently reported between 25% and 35%, and contribute significantly to disease-related mortality in these settings (12). Factors such as delayed presentation, limited diagnostic capacity for cytogenetic and molecular risk stratification, treatment interruptions, infectious complications, and socioeconomic barriers collectively undermine treatment success (13).

Relapsed ALL represents the leading cause of treatment failure and cancer-related death in children worldwide. Although only a minority of patients fail frontline therapy, the absolute burden of relapsed disease remains substantial, given the global incidence of ALL (8). The reappearance of leukemic blasts defines relapse after achieving complete remission. It is strongly associated with adverse biologic features, suboptimal early treatment response, and persistent minimal residual disease (1)(7). Established clinical predictors, including age at diagnosis and initial white blood cell count, remain relevant, but their prognostic performance may vary significantly across healthcare settings (1).

The management of relapse requires intensive salvage chemotherapy. Selected high-risk patients for hematopoietic stem cell transplantation. These approaches offer curative potential despite being associated with considerable treatment-related toxicity, long-term morbidity, and diminished quality of life (14). Survivors of relapse therapy frequently experience prolonged immunosuppression, recurrent infections, fatigue, and neurocognitive impairments that affect educational attainment and psychosocial development (15). Moreover, the protracted and resource-intensive nature of relapse treatment imposes substantial emotional, social, and financial burdens on affected families, particularly in resource-constrained environments (16).

In Ethiopia, pediatric cancer care is challenged by structural and systemic limitations. Although population-based cancer registry data are lacking, available institutional reports indicate that ALL is the most common childhood malignancy diagnosed in the country (17)(18). Delays in diagnosis are frequent due to limited public awareness, inadequate diagnostic infrastructure at peripheral health facilities, and prolonged referral pathways to specialized centers (19). At Tikur Anbessa Specialized Hospital, the primary national referral center for pediatric oncology, access to advanced diagnostic modalities such as

flow cytometry, cytogenetics, molecular testing, and MRD assessment remains limited by financial constraints, supply shortages, and workforce gaps (20).

In addition to diagnostic limitations, treatment abandonment and interruption represent significant threats to successful outcomes. Reported abandonment rates in Ethiopia are substantially higher than those observed in HICs, particularly among families from rural areas. These are driven by socioeconomic hardship, travel distance, and limited psychosocial support (21). The inadequacy of a comprehensive national cancer registry further restricts systematic monitoring of disease incidence, relapse patterns, and treatment outcomes, hindering evidence-based policy development and programmatic improvement (22).

Given these challenges, there is a critical need for locally generated evidence to characterize treatment outcomes and identify context-specific predictors of relapse among Ethiopian children with ALL. Understanding the relative contributions of clinical, biologic, and treatment-related factors in this setting is essential for refining risk stratification, optimizing resource allocation, and developing targeted interventions to improve survival and reduce disparities in pediatric ALL care.

1.2. Statement of the problem

Despite significant global advances in pediatric ALL management, substantial disparities in clinical outcomes persist between high-income and low- and middle-income countries (LMICs), including Ethiopia. Children diagnosed with ALL in resource-constrained settings face significantly higher risks of relapse and mortality. (23) (24)This elevated risk is primarily driven by a confluence of factors, including delayed diagnosis leading to advanced presentation, limited access to comprehensive diagnostic tools such as MRD monitoring and detailed cytogenetics, high rates of treatment abandonment, often linked to socioeconomic barriers, and systemic deficiencies within the healthcare infrastructure. (24–28)(26).

Although risk-adapted treatment protocols and sophisticated MRD monitoring have markedly improved prognostic accuracy and survival rates in HICs, these resource-intensive strategies remain largely inaccessible or are inconsistently implemented in

Ethiopia. Furthermore, the absence of a national cancer registry impedes accurate surveillance of disease incidence, relapse patterns, treatment effectiveness, and long-term outcomes on a population level (28–30).

Systematic, locally derived data on the specific predictors of relapse in pediatric ALL remain scarce at Tikur Anbessa Specialized Hospital, Ethiopia's primary pediatric oncology center. This critical evidence gap hampers the development and validation of context-specific risk stratification models and the design of tailored supportive care or therapeutic interventions(31–33). Without a clear understanding of the relative contributions of clinical, biological, treatment-related, and socioeconomic factors to relapse within this specific patient population, efforts to improve therapeutic outcomes, optimize the use of limited resources, and reduce the profound disparities in pediatric oncology care are severely limited.(32,34)

This study directly addresses this critical knowledge gap by retrospectively analyzing pediatric ALL cases treated at TASH to identify treatment outcomes and determine the magnitude and predictors of relapse within the Ethiopian context. The findings are intended to inform the adaptation or development of risk-adapted management strategies, guide clinical decision-making at the point of care, and support evidence-based policy initiatives to enhance outcomes for Ethiopian children diagnosed with ALL.(27,35,36)

1.3. Significance of the Study

Pediatric ALL relapse remains a significant cause of cancer-related morbidity and mortality among children globally, with pronounced and unacceptable disparities in outcomes between HICs and LMICs like Ethiopia. Despite ALL being a common pediatric malignancy encountered at TASH, context-specific data on relapse patterns, associated risk factors, and the impact of local systemic challenges remain limited.

By systematically identifying the clinical, biological, treatment-related, and socioeconomic predictors of relapse within the TASH patient cohort, this study directly addresses a critical national evidence gap. The findings will be crucial for informing the development or adaptation of contextually appropriate risk stratification frameworks. This allows for

more tailored therapeutic intensity, potentially sparing lower-risk patients from excessive toxicity while identifying higher-risk patients who might benefit from intensified therapy or closer monitoring, even within resource constraints. Furthermore, understanding predictors can guide targeted supportive care interventions and optimize institutional-level resource allocation strategies.

Moreover, the results will provide valuable, locally generated evidence for health policymakers and hospital administrators, potentially supporting strategic investments in diagnostic infrastructure, improving access to tests to better risk-stratify patients, strengthening referral pathways, enhancing pharmacy supply chains, and developing programs to mitigate treatment abandonment through patient navigation or psychosocial support. Ultimately, this study's contribution extends beyond the national context; by enriching the scientific discourse with robust data from an underrepresented LMIC setting, it supports broader global efforts to understand and reduce inequities in childhood cancer outcomes worldwide.

2. Literature review

2.1. Epidemiology of ALL

Acute lymphoblastic leukemia is the most common malignancy affecting children and adolescents, accounting for approximately one quarter of all pediatric cancers and nearly 75–80% of leukemia diagnoses in this age group worldwide (1)(37). Even though ALL is found worldwide, its epidemiology varies significantly by age, sex, ethnicity, and region, indicating complex interactions among genetics, environment, and healthcare factors.

The incidence of pediatric ALL is highest in high-income countries, where population-based cancer registries report annual rates ranging from 3 to 5 cases per 100,000 children younger than 15 years (9). A distinctive feature of ALL epidemiology is the pronounced age-specific incidence peak occurring in early childhood, particularly between 2 and 5 years of age. This peak is most evident in B-cell precursor ALL and is less prominent in T-cell ALL, which tends to present in older children and adolescents (1)(38). Following early childhood, incidence rates decline through late childhood and adolescence before rising again in adulthood.

Across most populations, pediatric ALL exhibits a consistent male predominance, with reported male-to-female ratios typically ranging from 1.2:1 to 1.4:1 (39). Sex-related differences are more pronounced in specific subtypes, particularly T-cell ALL, which is more common in males. Variations in incidence by ethnicity have also been well documented, particularly in studies from HICs. Children of Hispanic and White ethnic backgrounds have been reported to have higher incidence rates compared with children of African or Asian descent (1). These disparities are thought to arise from a combination of inherited genetic risk factors and differential environmental or early-life exposures, although the precise mechanisms remain incompletely understood (40).

Marked geographic differences in reported ALL incidence exist between HICs and low- and middle-income countries (LMICs). In many LMIC settings, reported incidence rates are substantially lower than those observed in HICs (11). However, this apparent difference likely reflects, at least in part, underdiagnosis, delayed presentation, limited access to diagnostic services, and incomplete cancer registration systems rather than

actual differences in disease occurrence (41). In the absence of comprehensive population-based registries, the actual burden of pediatric ALL in many LMICs remains underestimated.

Temporal trends in pediatric ALL incidence further illustrate epidemiologic complexity. Several long-term studies from HICs have demonstrated a modest but steady increase in ALL incidence over recent decades, particularly for B-cell precursor subtypes (42)(43). Proposed explanations include changes in environmental exposures, lifestyle factors, and patterns of early-life infections that may influence immune system development. Nonetheless, definitive causal pathways have yet to be established, and comparable trend data from LMICs are scarce.

While incidence provides insight into disease occurrence, prevalence has become increasingly relevant for improving survival. In HICs, dramatic advances in therapy have resulted in a growing population of childhood ALL survivors, many of whom face long-term treatment-related complications requiring ongoing medical follow-up (14)(44). In contrast, the prevalence of long-term survivors in LMICs is lower, reflecting reduced survival, higher treatment-related mortality, and substantial rates of treatment abandonment (45). These differences underscore the unequal global distribution of the burden of survivorship and the need for health system planning tailored to local epidemiology.

In Ethiopia, reliable population-based incidence and prevalence data for pediatric ALL are lacking due to the lack of a national cancer registry. Available information is derived primarily from institutional and regional reports, which consistently identify leukemia, predominantly ALL, as the most common childhood cancer diagnosed in the country (17)(18). However, these data likely underestimate the true incidence, particularly in rural and underserved regions, where access to diagnostic and referral services is limited. Improved epidemiologic surveillance is therefore essential to accurately define disease burden, guide resource allocation, and inform national childhood cancer control strategies.

2.2. Overview of ALL: Clinical, Laboratory, and Molecular Aspects

Acute Lymphoblastic Leukemia (ALL) manifests through a range of clinical features that stem from the underlying biology of uncontrolled lymphoid proliferation and subsequent bone marrow failure. A thorough understanding of both the patient's clinical presentation and the molecular aberrations driving the disease is essential for accurate diagnosis, appropriate risk stratification, and effective therapeutic planning.

Presenting complaints are typically non-specific and arise primarily from the infiltration of the bone marrow by leukemic blasts, which suppresses normal hematopoiesis. Consequently, patients commonly experience symptoms related to cytopenias: fatigue, pallor, and irritability due to anemia; easy bruising, petechiae, or bleeding episodes like epistaxis resulting from thrombocytopenia; and increased susceptibility to infections, often manifesting as persistent fever or recurrent illnesses, due to neutropenia(3) (1). Bone and joint pain can be a prominent feature, sometimes severe enough to cause limping or refusal to bear weight, attributed to leukemic expansion within the bone marrow cavity and periosteal infiltration. While less common than in other hematologic malignancies, systemic symptoms such as unexplained fever, weight loss, or night sweats may also occur. Physical examination often corroborates these symptoms, revealing pallor, cutaneous signs of bleeding, and frequently, lymphadenopathy and hepatosplenomegaly indicative of extramedullary leukemic spread(2). Testicular involvement in boys and central nervous system (CNS) infiltration, which can present with neurological symptoms or be clinically silent, represent other significant sites of potential extramedullary disease requiring specific diagnostic evaluation and management(41).

Initial laboratory investigations, particularly the complete blood count (CBC), typically show anemia and thrombocytopenia. The total white blood cell (WBC) count varies, ranging from low to markedly elevated (hyperleukocytosis), but examination of the peripheral blood smear often reveals circulating lymphoblasts. Definitive diagnosis necessitates bone marrow aspiration and biopsy, with confirmation based on morphological, cytochemical, and immunophenotypic analysis demonstrating ≥20% lymphoblasts, according to current classifications(46). Certain clinical and laboratory

parameters present at diagnosis carry significant prognostic weight and are crucial for initial risk assessment. These include the patient's age (with infants <1 year and those ≥10 years generally facing higher risks), the initial WBC count (where hyperleukocytosis often predicts poorer outcomes), the specific immunophenotype, the presence and extent of extramedullary disease (especially CNS or testicular involvement), and the rapidity and depth of response to initial therapy, most accurately measured by Minimal Residual Disease assessments (1)(9)(47).

The molecular pathogenesis of ALL involves a multi-step accumulation of genetic and epigenetic alterations within a lymphoid progenitor cell, disrupting standard controls over differentiation, proliferation, and survival.(9) (3). These molecular lesions define distinct ALL subtypes with differing biological behaviors and therapeutic sensitivities. Chromosomal rearrangements are particularly characteristic, often serving as initiating events. These include translocations that create oncogenic fusion genes, such as *BCR-ABL1* [t(9;22)], *KMT2A* rearrangements [e.g., t(4;11)], and *ETV6-RUNX1* [t(12;21)], each associated with specific prognoses and sometimes offering targets for therapy (e.g., tyrosine kinase inhibitors for *BCR-ABL1*). Aneuploidy, or abnormal chromosome numbers, is also significant; high hyperdiploidy generally correlates with favorable outcomes in B-ALL, whereas hypodiploidy is linked to inferior prognosis.(48)(49)(49) .

Complementing these large-scale chromosomal changes are sequence mutations—point mutations or small insertions/deletions—affecting genes critical for cellular function, which often accrue as secondary leukemogenic events. Frequently mutated genes include those encoding transcription factors essential for lymphoid development, such as *PAX5*, *IKZF1* (Ikaros), and *TCF3*, whose alteration impairs differentiation; deletions of *IKZF1* are notably associated with increased relapse risk (9)(47). Mutations also commonly occur in components of key cell signaling pathways, such as RAS-MAPK and JAK-STAT, which drive proliferation and survival, as well as in tumor suppressor genes such as *TP53* and *CDKN2A/B* (Roberts et al., 2014; Hof et al., 2011). Furthermore, genes involved in epigenetic regulation, including histone modifiers (*CREBBP*, *KMT2A*) and chromatin remodelers (e.g., INO80 complex members), are frequently mutated,

contributing to aberrant gene expression programs that sustain the malignant phenotype (9).

2.3. Pediatric ALL in Low- and Middle-Income Countries (LMICs): Challenges and Disparities

Remarkable progress in the treatment of pediatric acute lymphoblastic leukemia has transformed the disease into one with high cure rates in high-income countries, where long-term survival now exceeds 90%. In contrast, outcomes in low- and middle-income countries remain substantially inferior, with reported survival rates often below 60% and, in some settings, considerably lower (50).

Delayed diagnosis represents a major contributor to poor outcomes in LMICs. Limited public awareness of childhood cancer symptoms, inadequate training and diagnostic suspicion among primary healthcare providers, and prolonged referral pathways frequently result in children presenting at advanced stages of disease (19)(51). Consequently, many patients are diagnosed with high leukemic burden, severe cytopenias, malnutrition, or active infections, all of which increase early treatment-related morbidity and mortality and compromise tolerance to intensive chemotherapy (52).

Deficiencies in diagnostic capacity further exacerbate these challenges. While morphological diagnosis of ALL is often achievable, access to advanced diagnostic modalities, essential for accurate risk stratification, is severely constrained in many LMIC settings. Multi-parameter flow cytometry for immunophenotyping, cytogenetic analysis for detection of prognostically relevant chromosomal abnormalities, and molecular testing for recurrent gene fusions are frequently unavailable, inconsistently accessible, or financially prohibitive (20)(41). Moreover, routine assessment of minimal residual disease, a cornerstone of modern risk-adapted therapy in HICs, is rarely feasible in LMICs (7). As a result, treatment decisions are commonly based on limited clinical parameters, leading to suboptimal risk stratification and less individualized therapy.

Challenges in treatment delivery constitute another critical determinant of poor outcomes. In many LMICs, the availability of essential chemotherapeutic agents is inconsistent due

to procurement delays, supply chain disruptions, and financial constraints (53). Treatment interruptions and dose modifications are therefore common and may reduce therapeutic efficacy. Compounding these issues is the limited availability of comprehensive supportive care services. Restricted access to safe blood products, broad-spectrum antibiotics, antifungal agents, nutritional rehabilitation, and intensive care support significantly increases the risk of treatment-related mortality, particularly during intensive phases such as induction (13)(54). In some LMIC settings, deaths related to infection or toxicity rival or exceed relapse as the leading cause of treatment failure.

Treatment abandonment represents a particularly devastating challenge in pediatric oncology within LMICs. Abandonment rates exceeding 30–50% have been reported in several resource-constrained settings, in stark contrast to rates below 5% in HICs (21). Families may discontinue therapy due to financial hardship, long travel distances to treatment centers, loss of income, lack of accommodation, sociocultural beliefs, or inadequate understanding of the prolonged and intensive nature of ALL treatment. Treatment abandonment effectively precludes cure and significantly inflates mortality statistics, distorting survival estimates and undermining programmatic success.

Underlying these clinical barriers are broader systemic constraints, including shortages of trained pediatric oncologists, oncology nurses, pathologists, and laboratory specialists. Health systems in many LMICs also lack robust health information infrastructure, limiting the ability to monitor treatment outcomes, relapse patterns, and long-term survival. The absence of comprehensive, population-based cancer registries in most LMICs, including Ethiopia, hampers accurate estimation of disease burden and impedes evidence-based planning and policy development (17).

Recognizing these disparities, global initiatives have increasingly focused on improving childhood cancer outcomes in LMICs. International collaborations, institutional twinning programs, and the development of resource-stratified treatment guidelines aim to adapt effective therapies to constrained settings while minimizing toxicity (53). The World Health Organization’s Global Initiative for Childhood Cancer exemplifies such efforts to achieve at least 60% survival for children with cancer worldwide. However, the successful

implementation of these initiatives requires locally generated data to guide context-specific adaptations.

Importantly, prognostic models and treatment algorithms developed in HICs may not perform equivalently in LMIC environments. Factors such as malnutrition, endemic infections, treatment interruptions, and high abandonment rates can modify the prognostic significance of traditional risk factors, including age and leukocyte count (1)(36). Therefore, research conducted within LMIC settings is essential to identify locally relevant predictors of outcome and relapse. Such evidence is critical for developing feasible risk stratification strategies, optimizing resource utilization, and designing interventions that address the unique challenges faced by children with ALL in resource-limited contexts.

2.4. Treatment Abandonment: A Major Barrier

Treatment abandonment represents one of the most significant barriers to improving survival and relapse rates for pediatric ALL in Ethiopia. Reported abandonment rates are alarmingly high, estimated between 40% and 60%, particularly affecting families from rural areas or lower socioeconomic backgrounds(55). This starkly contrasts with rates below 5% in HICs. The complex drivers include the substantial direct and indirect financial burdens placed on families, long travel distances to Tikur Anbesa specialized hospital, lack of adequate accommodation and social support in Addis Ababa, communication barriers, and sometimes, a lack of complete understanding of the protracted nature of ALL therapy.(55). High abandonment rates preclude the possibility of a cure for a large proportion of diagnosed children. (21).

2.5. Relapse and Predictor Factors

Relapse remains the most significant cause of treatment failure and disease-related mortality in pediatric acute lymphoblastic leukemia, despite substantial improvements in frontline therapy. Although the majority of children achieve complete remission following induction chemotherapy, a clinically significant proportion subsequently experience disease recurrence, which is associated with markedly reduced survival and increased

treatment-related morbidity (1)(8). The burden of relapse is disproportionately higher in low- and middle-income countries, where limitations in diagnostic precision, treatment delivery, and supportive care compromise long-term disease control (12).

Relapse in ALL is defined by the re-emergence of leukemic blasts after the achievement of morphologic remission and may occur in the bone marrow, extramedullary sites, or both. Bone marrow relapse is the most common presentation and is generally associated with poorer outcomes compared with isolated extramedullary relapse, particularly when it occurs early during or shortly after completion of therapy (7). Central nervous system and testicular relapses, while less frequent, pose unique therapeutic challenges and often reflect inadequate initial disease control at sanctuary sites.

The timing of relapse is a critical determinant of prognosis. Early relapse, typically occurring within 18 months of diagnosis or during ongoing therapy, is consistently associated with inferior survival outcomes, reflecting underlying chemoresistance and aggressive disease biology (8). Intermediate and late relapses, occurring after completion of therapy, generally carry a more favorable prognosis but still require intensive salvage treatment. In LMICs, delayed recognition of relapse due to limited follow-up capacity and restricted access to diagnostic evaluations may further worsen outcomes.

Multiple clinical and biological factors have been identified as predictors of relapse in pediatric ALL. Traditional clinical predictors include age at diagnosis and initial white blood cell (WBC) count, both of which are incorporated into conventional risk stratification systems. Children younger than one year or older than ten years, as well as those presenting with markedly elevated WBC counts, have consistently demonstrated higher relapse risk (1). However, the prognostic value of these factors may vary across healthcare settings and treatment protocols.

Immunophenotype also influences relapse risk, with T-cell ALL historically associated with higher relapse rates compared with B-cell precursor ALL. Although contemporary treatment regimens have narrowed this gap in HICs, outcomes for T-cell ALL remain inferior in many LMIC settings, where intensified protocols and advanced supportive care may not be uniformly available (38). Additionally, male sex has been associated with an

increased risk of relapse in some studies, potentially related to sanctuary site involvement and pharmacokinetic differences, though findings have been inconsistent.

At the biological level, specific cytogenetic and molecular abnormalities play a central role in determining relapse risk. Favorable genetic features, such as high hyperdiploidy and ETV6-RUNX1 fusion, are associated with excellent treatment responses and low relapse rates. In contrast, adverse-risk abnormalities, including hypodiploidy, KMT2A rearrangements, BCR-ABL1 fusion, and deletions involving IKZF1, are strongly linked to treatment resistance and disease recurrence (4)(36). Unfortunately, routine detection of these abnormalities is often limited or unavailable in LMICs, restricting their use in risk-adapted therapy.

Early treatment response is among the most powerful predictors of relapse. In HICs, minimal residual disease assessment during induction and consolidation therapy has emerged as the single most important prognostic marker, surpassing traditional clinical factors (7). However, the absence of routine MRD testing in many LMIC settings necessitates reliance on less sensitive surrogate markers of response, such as morphologic remission status and peripheral blood count recovery, which may fail to identify high-risk patients.

Treatment-related factors also contribute significantly to relapse risk. Inadequate chemotherapy intensity, treatment delays, dose reductions, and premature discontinuation of therapy can compromise disease control and facilitate clonal persistence (53). In LMICs, these issues are frequently driven by drug stockouts, toxicity-related interruptions, infections, malnutrition, and socioeconomic barriers. Treatment abandonment, in particular, represents an extreme form of therapy failure and is often indistinguishable from relapse in survival analyses, further complicating outcome assessment (21).

Emerging evidence suggests that host-related factors, including nutritional status, comorbid infections, and treatment adherence, may modify relapse risk, particularly in resource-limited settings. Malnutrition has been associated with altered drug pharmacokinetics, increased toxicity, and impaired immune function, all of which may

contribute to inferior leukemia control (52). These factors are seldom incorporated into conventional risk models but may be highly relevant in LMIC populations.

2.6. Molecular Markers and Genetic Predictors of Relapse

The accurate prediction of relapse risk in pediatric Acute Lymphoblastic Leukemia has been significantly advanced by the identification and integration of specific molecular and genetic markers into risk stratification algorithms, particularly in high-income countries.(47). These biological features, encompassing cytogenetic abnormalities, specific gene fusions, copy number alterations, and gene mutations, provide crucial insights into leukemia biology, chemoresistance, and patient prognosis, allowing for the refinement and tailoring of treatment.(7).

Established cytogenetic abnormalities are fundamental predictors of outcome. Ploidy, the number of chromosomes in leukemic cells, is a significant factor, with high hyperdiploidy generally conferring a favorable prognosis in B-cell precursor ALL. In contrast, hypodiploidy signifies a very high risk of relapse. Specific chromosomal translocations creating recurrent gene fusions also carry significant prognostic weight. The *BCR-ABL1* fusion (Philadelphia chromosome, t(9;22)), while historically indicating poor outcomes, now represents a high-risk feature manageable with the addition of tyrosine kinase inhibitors (TKIs) (47)(9) the *ETV6-RUNX1* fusion (t(12;21)), the most common alteration in childhood B-ALL, is associated with an excellent prognosis(47). Rearrangements involving the *KMT2A* gene (11q23), prevalent in infants, generally portend a poor prognosis(9).

2.7. Burden and Diagnosis of Pediatric ALL in Ethiopia

The challenges characterizing pediatric Acute Lymphoblastic Leukemia management in low- and middle-income countries are acutely reflected in Ethiopia. As established from institutional and regional data, ALL represents the most common pediatric malignancy diagnosed in the country(17)(18). However, the true incidence and prevalence remain uncertain due to the absence of a comprehensive, population-based national cancer registry (17). Current understanding relies heavily on data extrapolated from major

treatment centers, primarily TASH in Addis Ababa, the nation's principal referral hospital for pediatric oncology.

Diagnostic capabilities, while improving, face significant constraints. Delays in diagnosis are common, often stemming from limited awareness among the public and primary healthcare providers, inadequate diagnostic facilities at peripheral health centers, and complex, lengthy referral processes to reach specialized care(51). At tertiary centers like BLSH, access to essential diagnostic tools for comprehensive ALL workup remains limited and inconsistent. While morphological diagnosis is standard, crucial techniques such as multi-parameter flow cytometry for accurate immunophenotyping, cytogenetic analysis for identifying key prognostic chromosomal abnormalities, and molecular testing for specific genetic lesions are often restricted by cost, reagent availability, equipment maintenance issues, and shortages of trained laboratory personnel(20) . The capacity for routine Minimal Residual Disease monitoring, a cornerstone of risk-adapted therapy in high-income countries, is largely absent or accessible only on a limited, often research-driven, basis (20). This lack of detailed diagnostic and prognostic information severely hampers the ability to implement contemporary risk stratification algorithms effectively, often necessitating the use of less tailored treatment approaches based primarily on clinical parameters.

2.7.1. Applicability of advanced diagnostics in the Ethiopian Context

Despite the established prognostic significance of these molecular and genetic markers in HICs, their practical application in guiding risk stratification and predicting relapse in Ethiopia is severely constrained. As previously discussed, routine access to the necessary diagnostic technologies – including comprehensive cytogenetics, FISH or PCR for specific gene fusions, genomic profiling for CNAs like *IKZF1* deletions, and critically, standardized MRD monitoring – is largely unavailable at centers like BLSH due to resource limitations(20) (50). This forces reliance on less precise risk stratification based mainly on clinical features (age, initial WBC count) and morphological response(12)(13) . This diagnostic gap prevents the effective tailoring of therapy based on underlying biology and creates a significant knowledge gap regarding the true prevalence and prognostic

impact of these genetic alterations within the Ethiopian pediatric ALL population, making it difficult to ascertain whether these markers hold the same predictive power or if other factors dominate relapse risk in this specific, resource-constrained setting (13)(41).

2.8 Treatment of relapsed leukemia

The treatment for relapsed ALL is intensive chemotherapy followed by allogeneic Hematopoietic Stem Cell Transplant (HSCT) for patients who have an early bone marrow relapse or suboptimal response to reinduction chemotherapy. Standard reinduction chemotherapy includes an anthracycline combined with vincristine, asparaginase, prednisone or dexamethasone, and Central nervous system (CNS) directed therapy(57). Twelve months of intensive systemic chemotherapy with reduced-dose cranial radiation (18 Gy) is highly effective for children with isolated CNS relapse and CR1 of 18 months or more. Novel strategies are needed for patients with CR1 of less than 18 months(58). The ALL R3 showed an improvement in outcome for CNS relapses treated with Mitoxantrone compared to Idarubicin; a potential benefit for matched donor transplant for those with very early and early isolated-CNS relapses. (59) A 5-year overall survival rate of 73.1% ± 8.3% was achieved in children with first isolated testicular relapse (ITR) of B-ALL occurring more than 18 months after initial complete remission (CR1), when treated with intensive chemotherapy while minimizing testicular radiation. (58)

2.9. Implications and Need for Local Research

Collectively, factors such as delayed presentation, limited diagnostic capacity, challenges in treatment delivery, inadequate supportive care, and extremely high abandonment rates create a problematic environment for managing pediatric ALL in Ethiopia(50) (54). Consequently, outcomes lag behind HICs, with relapse and TRM as major contributors to treatment failure. (12). The unique interplay of these factors suggests HIC prognostic models may have different predictive weights in Ethiopia.(1) .

Crucially, there is a significant paucity of systematic studies investigating relapse predictors specifically among Ethiopian pediatric ALL patients. Existing institutional data from BLSH require comprehensive analysis to identify key drivers of relapse, considering diagnostic limitations and systemic challenges. Relapse rates in Ethiopia are estimated

at 25-35%(12) , fueled by factors including limited MRD access, treatment interruptions, and socioeconomic barriers impacting adherence (39). This underscores the critical need for local research, such as the present study, to identify specific clinical, biological (where available), and socioeconomic predictors of relapse at BLSH. Such knowledge is essential for developing contextually appropriate risk stratification, improving adherence, reducing abandonment, optimizing resource allocation, and ultimately enhancing survival outcomes in Ethiopia. (39).

3. Research Objectives

3.1. General Objective

- To assess outcomes of pediatric acute lymphoblastic leukemia and identify key clinical, biological, treatment-related, and socioeconomic predictors for outcomes among patients treated at TASH.

3.2. Specific Objectives:

- To describe the baseline characteristics and treatment outcomes of pediatric acute lymphoblastic leukemia patients managed at Tikur Anbessa Specialized Hospital.
- To evaluate the associations between sociodemographic factors, baseline clinical characteristics, and therapeutic variables with the occurrence of relapse and death
- To characterize survival and event patterns in pediatric ALL patients at initial diagnosis and following relapse.

4. Research methodology and design

4.1. Research Design

This study adopts a quantitative, retrospective cohort design to investigate treatment outcomes in acute lymphoblastic leukemia and the burden of relapse, along with associated predictors, among pediatric patients diagnosed with Acute Lymphoblastic Leukemia and treated at Tikur Anbesa Specialized Hospital in Addis Ababa, Ethiopia. The approach involves identifying eligible patients diagnosed within a defined timeframe and systematically reviewing their historical medical records to extract relevant data on predictor variables, including clinical characteristics, available biological markers, treatment-related factors, and socioeconomic status. These variables, recorded at diagnosis or during the treatment period, will be assessed in relation to subsequent relapse status and time-to-relapse.

The retrospective cohort design is particularly well-suited for examining associations between baseline or time-varying exposures and the risk of relapse within a clearly defined patient population, utilizing pre-existing longitudinal data. This methodology is both methodologically sound and operationally feasible within a resource-constrained healthcare setting. The primary outcome of interest is patient and disease profile, overall survival, relapse-free survival (RFS), and their associated factors.

4.2. Study Setting and Population

The study will be conducted at the Pediatric Oncology Unit of TASH, including inpatient wards and outpatient follow-up clinics. TASH is the largest tertiary referral hospital in Ethiopia and the primary center for pediatric cancer care in the country. The study population will comprise all pediatric patients aged < 18 years at diagnosis who were newly diagnosed with ALL between September 2020 and September 2025. This timeframe provides a sufficient sample size and an adequate follow-up duration to observe outcomes and relapse events. Consecutive eligible patients meeting these criteria within the study period will be included to minimize selection bias.

4.3. Sample Size Determination

The sample size was calculated based on the expected relapse rate in children with ALL. Previous studies in LMICs, including Ethiopia, report relapse rates of approximately 25–35%. Assuming an expected relapse rate of 30%, a 95% confidence

level, and a margin of error of 5%, the sample size for estimating the proportion of relapse was calculated using the formula for a single proportion:

$$n = \frac{Z^2 \cdot P \cdot (1 - P)}{d^2}$$

Where:

$Z = 1.96$(for 95% confidence)

$P = 0.30$(expected proportion of relapse)

$d = 0.05$(margin of error)

$$n_0 = \frac{Z^2 p(1-p)}{d^2} \quad n_0 = \frac{\left((1.96)^2 \times 0.30 \times 0.70\right)}{0.0025} = 318$$

A finite population correction (N = 620) was applied:

$$n_{FPC} = \frac{n_0}{1 + \frac{n_0 - 1}{N}} \; n_{FPC} = \frac{318}{1 + \frac{317}{620}} = 210.4$$

Adjusting for 20% incomplete or missing records:

$$n_{final} = \frac{210.4}{0.80} = 263$$

4.4. Inclusion criteria

- Confirmed diagnosis of ALL based on morphology and available immunophenotyping
- Age within the specified range at diagnosis
- Initiation of ALL treatment at TASH according to institutional protocols

- Availability of core medical record data

4.5. Exclusion criteria

- Patients with ambiguous diagnoses or confirmed mixed-phenotype acute leukemia, unless specifically analyzed
- Patients who received the receiving more than half of their initial therapy outside TASH
- Records with grossly insufficient data to determine baseline characteristics or outcomes
- Patients with Down syndrome

4.6. Data Collection Techniques

This study has utilized retrospective medical record abstraction as its data collection technique. The process commenced with identifying eligible patient records from the specified timeframe using hospital charts, electronic records, and pediatric oncology unit logbooks, TASH. Following identification, the core data sources, predominantly paper-based medical charts, were retrieved from the medical records department, supplemented by any relevant information available in auxiliary electronic systems.

The cornerstone of the data collection process is a standardized data collection form, meticulously designed to capture all predefined study variables with clear definitions. Trained data collectors will employ this instrument to conduct a manual review of each patient's chart. This systematic review involved carefully examining various sections of the medical record, including admission notes, physician and nursing progress notes, laboratory results, consultation reports, chemotherapy flowsheets, and discharge summaries, to locate and extract the required information accurately. The use of trained personnel is crucial for ensuring consistency in interpretation and abstraction across all records.

Once abstracted onto paper forms, the data were entered into a secure electronic database using SPSS 27, and data analysis was conducted using R. To enhance data

fidelity, techniques such as double data entry for a subset of records or the implementation of validation rules within the database software were employed. Integrated quality control measures are vital throughout the process. These include pilot testing the data collection form, providing ongoing supervision and support to data collectors, and conducting periodic reviews of abstracted forms for completeness and consistency.

4.7. Data Analysis

Data has been analyzed using R statistical software. Descriptive statistics were summarized with patient demographics, clinical characteristics, treatment details, and outcomes. Continuous variables will be reported as mean ± SD or median with interquartile range, and categorical variables as frequencies and percentages.

Time-to-event outcomes, including overall survival (OS) and relapse-free survival (RFS), will be estimated using Kaplan–Meier methods. The Cox proportional hazards model was used for univariate and multivariate analyses to identify independent predictors of relapse and mortality. Variables with clinical relevance or $p < 0.25$ in univariate analysis will be included in multivariate models. Hazard ratios (HR) with 95% confidence intervals (CI) will be reported. The proportional hazards assumption will be assessed using Schoenfeld residuals, and statistical significance will be set at $p < 0.05$.

4.8. Ethical Considerations

Ethical approval will be obtained from the REC of the Department of Pediatrics and Child Health, College of Health Sciences, Addis Ababa University. As the study involves retrospective review of existing medical records, a waiver of individual informed consent will be requested, contingent on ensuring patient confidentiality. All data abstracted will be fully anonymized using unique study identifiers, and the database will be stored securely, accessible only to the research team.

4.9. Dissemination of Findings

The results of the study have been presented at the research defense in the département of Pediatrics and Child Health, and a formal report will be submitted to the DPCH. The research output will also be published in local or international peer-reviewed scientific journals and shared with governmental agencies to improve access to health services, including chemotherapy drugs and essential supportive care.

4.10. Operational definitions

- **Pediatric Acute Lymphoblastic Leukemia:** An individual below 18 years at the time of initial ALL diagnosis, identified through TASH records. Diagnosis must be documented based on bone marrow morphology.
- **Relapse:** The primary outcome event; operationally defined as the first documented reappearance of leukemia after achieving Complete Remission.
- **Risk Stratification:** The initial risk group, Standard Risk, High Risk, and intermediate risk, is assigned to the patient based on the criteria documented as per NCI risk classification.
- **Relapse-Free Survival (RFS):** A primary time-to-event outcome measure; defined as the time duration from the date of achieving initial Complete Remission (CR) to the date of first Relapse or the date of last follow-up/data cut-off if relapse-free (censored).
- **Overall Survival (OS):** A key secondary time-to-event outcome measure; defined as the time duration from the date of initial ALL diagnosis to the date of death from any cause or the date of last follow-up if alive (censored).
- **Treatment abandonment** is defined as failing to start or continue treatment for four or more consecutive weeks without a medical reason.
- **Laboratory TLS is** defined by the presence of two or more specific lab abnormalities (hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia) within a 3-day window before or a 7-day window after starting treatment.

- **Clinical TLS is** defined when laboratory TLS is present along with signs of significant clinical toxicity requiring intervention, such as acute kidney injury, cardiac arrhythmias, or seizures**.**
- **Lymphadenopathy:** one or more enlarged lymph nodes on physical examination or ultrasound attributed to disease presentation.
- **Liver involvement:** ultrasonographic or physical findings of hepatomegaly attributed to disease presentation
- **Splenic involvement,** ultrasonographic or physical findings of splenomegaly attributed to disease presentation
- **Testicular involvement:** ultrasonographic or physical findings of testicular enlargement attributed to disease presentation
- **Mediastinal involvement:** radiographic findings of mediastinal mass attributed to disease presentation
- **Renal involvement:** ultrasonographic or physical findings of renal enlargement attributed to disease presentation
- **Cancer death** is defined when cancer is identified as the underlying cause of death, the health condition that began the chain of events leading directly to the person's death.
- **Treatment interruption:** a treatment interruption is an unplanned temporary pause in therapy due to various causes

5. Results

5.1. Demographics and clinical characteristics

During the 5-year study period , 251 children diagnosed with acute lymphoblastic leukemia were included in the cohort. The children's ages ranged from 3 months to 17 years, with a mean age of 6.24 years (SD = 3.33). The majority of participants (206, 82.1%) were aged 1–10 years.

Of the 251 participants, 152 (60.6%) were male. With a male-to-female ratio of (1:1.5). The Majority of the children were from the Oromia region (40.6%), followed by Addis Ababa (20.6%). Most caregivers reported a monthly income between 4,000 and 8,000 ETB. Additionally, the majority of participants (77.3%) received support from the support group TAPPCO. The mean follow-up duration was 20.1 months (SD = 18 months).

Table 1: Comprehensive Patient Demographics and Clinical Data of pediatric ALL patients treated at TASH from 2020 to 2025

Variable	Category	Frequency	Percentage / Mean ± SD
Total participants	-	251	-
Age (years)	-	-	6.24 ± 3.33
Age group	Less than 1 year	5	0.1%
	1–10	206	82.1%
	10–18	45	17.9%
Sex	Male	152	60.6%
	Female	99	39.4%
Residence	Addis Ababa	43	17.1%
	<100 km from AA	22	8.8%
	100–300 km from AA	59	23.5%

Variable	Category	Frequency	Percentage / Mean ± SD
	300–600 km from AA	101	40.2%
	>600 km from AA	26	10.4%
Region	Oromia	102	40.6%
	Addis Ababa	51	20.3%
	Amhara	43	17.1%
	South Ethiopia	15	6.0%
	Central Ethiopia	19	7.6%
	Somali	8	3.2%
	South West Ethiopia	5	2.0%
	Sidama	5	2.0%
	Afar	2	0.8%
	Benishangul	1	0.4%
Caregivers' highest level of education	No formal education	89	35.5%
	Primary school	68	27.1%
	Secondary school	65	25.9%
	Higher education	29	11.6%
Caregivers' monthly income (ETB)	<4,000	33	13.1%
	4,000–8,000	101	40.2%
	8,000–12,000	96	38.2%
	>12,000	21	8.4%

Variable	Category	Frequency	Percentage / Mean ± SD
Support from TAPPCO	Yes	194	77.3%
	No	57	22.7%
Follow-up duration (months)	-	-	20.1 ± 18

5.2. Initial Clinical Presentation and Physical Findings

Children diagnosed with acute lymphoblastic leukemia commonly present with systemic symptoms. Fever was the predominant symptom (30.7%), followed by malaise (21.5%).

The mean duration of symptoms before presentation was 5.67 weeks (SD 5.28). Symptoms lasted more than 6 weeks in 29.5%. Nutritional assessment showed 26.7% had moderate acute malnutrition and 15.9% had severe acute malnutrition. Physical examination and imaging findings indicated that lymphadenopathy was present in 85.7%of children. Splenic involvement was observed in 74.5%, liver involvement in 79.7%, renal involvement in 8.8%, and mediastinal mass in 6.4%.

Table 2: Initial Clinical Presentation and Physical Findings of pediatric ALL patients treated at TASH from 2020-2025

Category	Feature	Frequency	Percentage
Presenting symptom	Fever	77	30.7%
	Malaise	54	21.5%
	Lymphadenopathy	34	13.5%
	Bone and joint pain	20	8.0%
	Bleeding	15	6.0%
	Cough	15	6.0%
	Abdominal swelling	14	5.6%
	Body swelling	8	3.2%
	Lower extremity weakness	4	1.6%
	Vomiting	3	1.2%
	Abdominal pain	3	1.2%
	Pallor	1	0.4%
	Chest pain	1	0.4%
	Seizure	1	0.4%
	Shortness of breath	1	0.4%
Duration of Symptoms	<2 weeks	24	9.6%
	2–6 weeks	153	61.0%
	>6 weeks	74	29.5%
Nutritional Status	Normal	144	57.4%
	Moderate acute malnutrition	67	26.7%
	Severe acute malnutrition	40	15.9%
Physical Examination and Imaging Findings	Lymphadenopathy	215	85.7%
	Testicular involvement	2	0.8%

Category	Feature	Frequency	Percentage
	Splenic involvement	187	74.5%
	Liver involvement	200	79.7%
	Renal involvement	22	8.8%
	Mediastinal mass	16	6.4%

5.3. Laboratory and pathologic findings

At diagnosis, the majority of children (45.2%) had a white blood cell count less than 20,000/μL. WBC counts of 20,000–50,000/μL and 50,000–100,000/μL were each observed in 46 children (18.4% each), with a median count of 23,000 (IQR 63,600). Hemoglobin levels were low in most children; 47.2% had hemoglobin <7 g/dL, and 44.0% had hemoglobin between 7–10 g/dL (mean 7.07, SD 2.11). Platelet counts were also frequently reduced, with 55.4% having 10,000–50,000/μL, and 21.9% having 50,000–100,000/μL(median 32,000, IQR 48,500).

Lactate dehydrogenase was elevated in most children, with 62.5% having levels of 250–1000 U/L and 31.5% having levels>1000 U/L (median IQR 689). Serum uric acid was <8 mg/dL in 74.1%, while 25.9% had levels >8 mg/dL (mean 6.68, SD 3.13). Tumor lysis syndrome at presentation was uncommon, with 81.7% having no TLS.

According to the FAB classification, 55.4% had L1 morphology, and 19.9% had L2 morphology. Immunophenotyping was performed in only 6% of 4 children; 1.6% were T-cell, 11 4.4% B-cell. Methods used included immunohistochemistry (26%) and flow cytometry (74%). Cytogenetic testing was only performed in 0.8% of children for BCR-ABL testing. Most children (92.8%) were classified as CNS1 at diagnosis, 0.8% as CNS2. Traumatic lumbar puncture was reported in 10.6%; among these, 12 were classified as CNS positive.

Table 3: Laboratory and pathologic findings of pediatric ALL patients treated at TASH from 2020 to 2025

Category/ Test	Parameter/ Finding	Frequency (n)	Percentage (%)	Median(IQR)
WBC Count (/μL)	-	-	-	23,000(63,600)
	<20,000	113	45.2%	-
	20,000–50,000	46	18.4%	-
	50,000–100,000	46	18.4%	-
	>100,000	45	18.0%	-
Hemoglobin (g/dL)	-	-	-	7.07 (2.11)
	<7	118	47.2%	-
	7–10	110	44.0%	-
	10–12	20	8.0%	-
	>12	2	0.8%	-
Platelet Count (/μL)	-	-	-	32,000 (48,500)
	<10,000	30	12.0%	-
	10,000–50,000	139	55.4%	-
	50,000–100,000	55	21.9%	-
	100,000–150,000	13	5.2%	-
	>150,000	14	5.6%	-
LDH (U/L)	-	-	-	689(724).
	<250	15	6.0%	-
	250–1000	157	62.5%	-
	>1000	79	31.5%	-
Uric Acid (mg/dL)	-	-	-	6.68 (3.13)
	<8	186	74.1%	-
	≥8	65	25.9%	-

Category/ Test	Parameter/ Finding	Frequency (n)	Percentage (%)	Median(IQR)
Tumor Lysis Syndrome (TLS)	No	205	81.7%	-
	Laboratory TLS	40	15.9%	-
	Clinical TLS	6	2.4%	-
FAB Classification	L1	139	55.4%	-
	L2	50	19.9%	-
	Undetermined	62	24.7%	-
Immunophenotype	Not done / available	236	94.0%	-
	T-cell	4	1.6%	-
	B-cell	11	4.4%	-
Method of Phenotyping	IHC	4	1.6%	-
	Flow cytometry	11	4.4%	-
Cytogenetic Testing	Not performed	249	99.2%	-
	Performed	2	0.8%	-
CNS Status at Diagnosis	CNS1	233	92.8%	-
	CNS2	2	0.8%	-
	CNS3	11	4.4%	-
	Unknown	5	2.0%	-
Traumatic Tap	No	219	89.4%	-
	Yes	26	10.6%	-

5.4. Treatment and treatment response

All patients received treatment according to the COG-adapted protocol based on their risk status. At the time of diagnosis, slightly more than half of the cohort (52.2%) were classified as standard risk, while 47.4% were high risk according to the NCI classification.

Treatment interruptions were documented in 31.9% of patients. Interruptions occurred most frequently during the maintenance phase (43%), followed by induction (25.8%) and consolidation (23.7%). The primary reasons for interruptions were severe infection (47.3%) and severe neutropenia (33.3%). Early treatment response was generally favorable. Prednisolone response was good in 80.1% of patients. Bone marrow evaluation at the end of induction showed that 76.1% of patients achieved M1 status.

Table 4: Treatment and treatment response of pediatric ALL patients treated at TASH from 2020 to 2025

Category	Subcategory	Count	Percentage
Treatment Protocol Received	COG adapted protocol	251	100%
Risk Status at Diagnosis	Standard Risk	131	52.2%
	Intermediate Risk	1	0.4%
	High Risk	119	47.4%
Documented Treatment Interruptions	No	171	68.1%
	Yes	80	31.9%
Phase of Treatment Interruption	Induction	24	25.8%
	Consolidation	22	23.7%
	Interim Maintenance	3	3.2%
	Delayed Intensification	4	4.3%
	Maintenance	40	43.0%
Reason for Treatment Interruption	Severe Infection	44	47.3%
	Severe Neutropenia	31	33.3%
	Severe Thrombocytopenia	6	6.5%
	Drug Unavailability	4	4.3%
	Failure to Attend Follow-up	3	3.2%

Category	Subcategory	Count	Percentage
	Severe Toxicity	1	1.1%
	Refusal to Take Medication	1	1.1%
	Hepatitis	1	1.1%
	Pancreatitis	1	1.1%
	Inadequate Blood Products	1	1.1%
Prednisolone response	Good	201	80.1%
	Poor	8	3.2%
	Not Done	37	14.7%
	Died Before Determination	5	2.0%
Bone Marrow Status at End of Induction	M1	191	76.1%
	M2	5	2.0%
	Not Diagnostic	3	1.2%
	Died Before Determination	39	15.5%
	On Induction	6	2.4%

5.5. Treatment Abandonment

Treatment abandonment was reported in 11.2% of patients. Among the patients who abandoned therapy, the leading reasons included financial difficulties in27.6%, opting for religious healing in 20.7%, and family issues in 20.7%. Community unrest contributed to 13.8% of cases.

Table 5: Treatment abandonment and attributed reasons of pediatric ALL patients treated at TASH from 2020 to 2025

Variable	Category	Count	Percentage
Treatment abandonment occurred	No	223	88.8%
	Yes	28	11.2%
Reason for abandonment	Financial issues	8	27.6%
	Religious healing	6	20.7%
	Family issues	6	20.7%
	Community unrest	4	13.8%
	Too far to come	2	6.9%
	Poor prognosis	2	6.9%
	The parent is afraid of toxicity	1	3.4%

5.6. Disease-related mortality

In this cohort, 35.2% of patients died. The leading cause of death was severe infection, accounting for 46.2% of deaths, and intracranial hemorrhage in15.4%. Less frequent causes included leukostatic lung injury and pulmonary hemorrhage; 32% of deaths had unknown causes since they happened at home or other health care settings where the cause of death can not be ascertained. Most deaths occurred in the oncologic ward (38.5%), followed by home deaths in 19.8%. Regarding the phase of treatment during which death occurred, the majority were during induction in 30.8%, followed by patients who had abandoned therapy in 18.7%.

Table 6: causes of disease-related mortality and characteristics of pediatric ALL patients treated at TASH from 2020 to 2025

Variable	Category	Count	Percentage
Death occurred	No	162	64.8%
	Yes	88	35.2%
Cause of death	Severe infection	42	46.2%

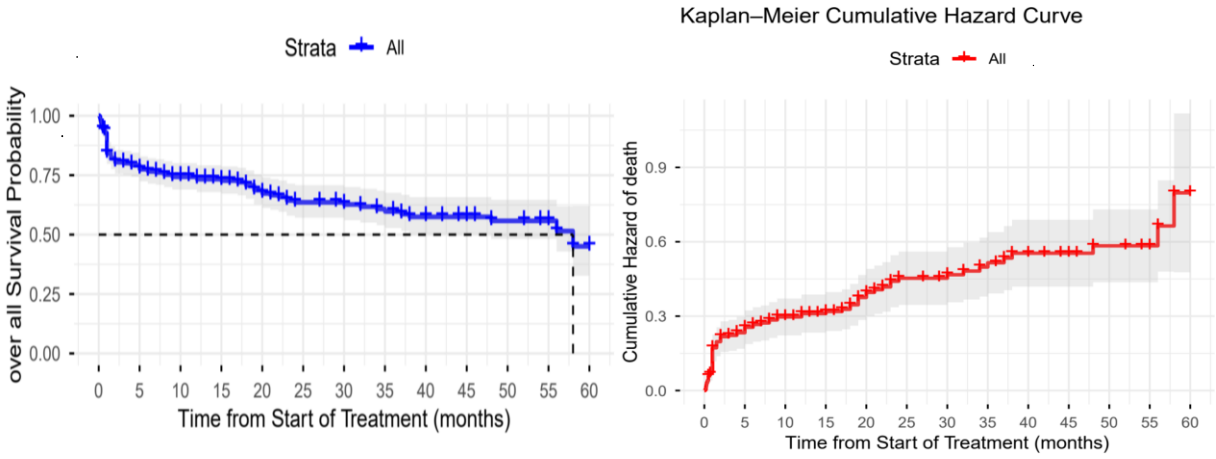
Variable	Category	Count	Percentage
	Unknown	29	31.9%
	Intracranial hemorrhage	14	15.4%
	Leukostatic lung injury	3	3.3%
	Pulmonary hemorrhage	3	3.3%
Where death occurred	Oncology ward	35	38.5%
	Home	18	19.8%
	Emergency unit	15	16.5%
	Other healthcare settings	15	16.5%
	ICU	8	8.8%
Phase of treatment during death	Induction	28	30.8%
	Abandoned	17	18.7%
	Prephase	10	11.0%
	Reinduction	9	9.9%
	Maintenance	8	8.8%
	Delayed intensification	7	7.7%
	Palliative oral chemotherapy	5	5.5%
	Consolidation	4	4.4%
	Interim maintenance	2	2.2%
	Completed therapy	1	1.1%

5.6.1. Time-to-Event Analysis for Mortality

Survival for this cohort of 251 patients declined rapidly during the first month, down to 84.2%, reflecting a high early mortality burden. After this steep initial decline, survival continued to decrease more gradually over time, reaching 80.5% at two months and 75.2% by month eight. The curve then showed a steady downward trend through the first two years, with survival at 63.6% by month 24. Beyond 2 years, declines were smaller but continued progressively, reaching 55.8% at month 48 and then falling suddenly to 45.1% by month 55, reflecting very small cohorts remaining in the study under our

observation. Overall, the data demonstrate high early mortality, followed by a slow, continuous decline, with approximately 45% of patients surviving at five years.

Figure 1: Time-to-Event Analysis of Mortality: Kaplan–Meier Survival and Cumulative hazard curves of pediatric ALL patients treated at TASH from 2020 to 2025



5.6.2. Predictors of time to death

In the Bi-variable Cox proportional hazards analysis, several variables had p-values <0.25 and were therefore included in the multivariable Cox regression model. These variables included TLS at presentation, treatment abandonment, age at presentation, risk status, WBC count, prednisolone response, bone marrow status at the end of induction, nutritional status at diagnosis, CNS status, and presenting symptoms.

After adjusting for potential confounders in the multivariable Cox proportional hazards model, two variables remained statistically significant independent predictors of mortality. Patients younger than one year at presentation had a significantly higher hazard of death compared to older children. Similarly, treatment abandonment was independently associated with an increased risk of death.

children presenting before 1 year of age had 4.58-fold risk of death compared with those aged >10 years, (AHR=4.58;95% CI: 3.13–6.71; $p < 0.00001$). Compared with patients aged 1–10 years, infants had an even higher risk of death, with an 11.1-fold increased risk (AHR = 11.1; 95% CI: 6.30–19.55; $p < 0.00001$). Patients who abandoned treatment

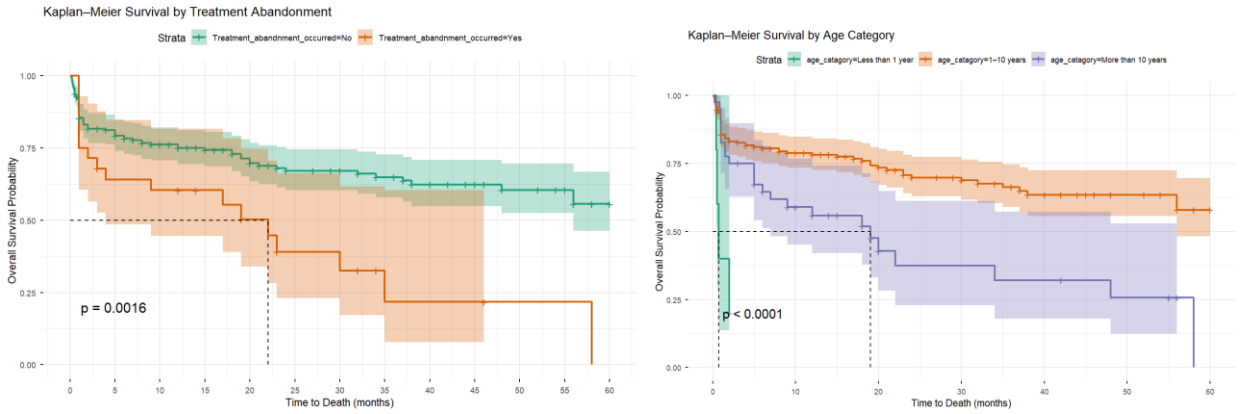
were at a 2.43-fold higher risk of death compared with those who completed therapy (AHR = 2.41; 95% CI: 1.19–4.88; *p* = 0.014).

Table 7**:** Bi-variable and Multivariable Cox Proportional Hazard Model death for patients on treatment of pediatric ALL patients treated at TASH from 2020 to 2025

Variable	Category	CHR (95% CI)	P-value	AHR (95% CI)	P-value
Age (years)	<1	1	–	1	–
	1–10	0.090 (0.029–0.281)	<0.001	0.018 (0.010–0.032)	<0.001
	>10	0.218 (0.067–0.711)	0.012	0.036 (0.019–0.066)	<0.001
Treatment abandonment	Yes	2.307 (1.353–3.933)	0.002	2.412 (1.192–4.881)	0.014
	No	1	–	1	–
TLS	Clinical	2.918 (1.061-8.028)	0.03	0.32(0.063–1.658)	0.176
	Laboratory	1.575 (0.935-2.654)	0.08	1.00(0.356-2.887)	0.986
	No	1		1	
CNS status	CNS 3	3.354 (1.563–7.196)	0.002	2.854 (0.970–8.393)	0.057
	CNS 2	3.465 (0.477-25.137)	0.2189	2.86329 (0.178557-45.914776)	0.457
	CNS 1	1	–	1	–
Category of WBC at diagnosis	50,000–100,000	1.890 (1.071–3.338)	0.028	1.275 (0.672–2.420)	0.458
	>100,000	2.936 (1.716–5.022)	<0.001	1.234 (0.630–2.420)	0.539
	20,000-50,000	0.701 (0.345-1.423)	0.325	0.74(0.297-1.839)	0.517
	<20,000 (ref)	1	–	1	–

Variable	Category	CHR (95% CI)	P-value	AHR (95% CI)	P-value
Nutritional status	SAM	2.074 (1.214–3.544)	0.008	0.751 (0.366–1.540)	0.434
	MAM	0.987 (0.589-1.658)	0.961	1.023 (0.458-2.282)	0.955
	Normal	1	–	1	–
Bone marrow status at the end of induction	M2	inf	<0.001	–	–
	M1	1	–	–	–
Prednisolone response	Poor	inf	<0.001	–	–
	Good	–	–	–	

Figure 2: Kaplan–Meier survival curves for death with Abandonment status and age category of pediatric ALL patients treated at TASH from 2020 to 2025



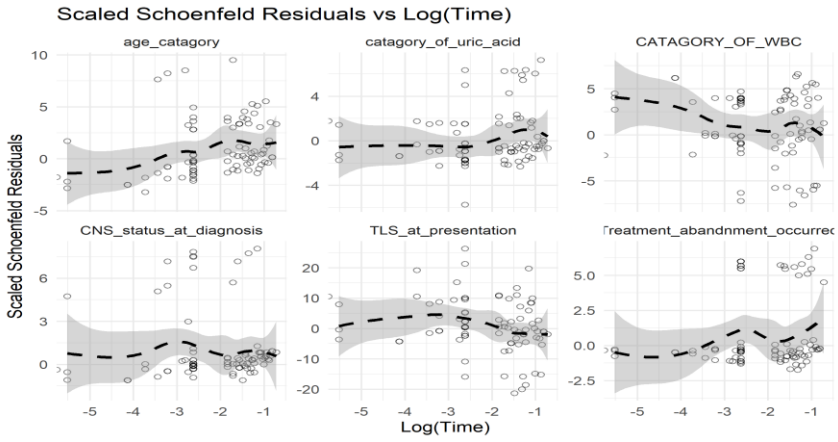
5.6.3. Test of proportional hazard assumption

The proportional hazards assumption of the Cox model was assessed using Schoenfeld residuals. No covariates violated the assumption (all p > 0.05), and the global test was non-significant (p = 0.113), indicating an adequate model fit. Graphical assessment of scaled Schoenfeld residuals also showed no systematic deviations, supporting the reliability of the estimated hazard ratios over time.

Table 8: Proportional Hazards Test Table of pediatric ALL patients treated at TASH from 2020-2025

Variable	Chi-sq	df	p-value
Category of WBC count	3.0879187	3	0.37826748
TLS at presentation	1.4824374	2	0.47653281
Treatment abandonment occurred	2.5609765	1	0.10953091
Age category	5.7999735	2	0.05502395
CNS status at diagnosis	0.4127346	3	0.93759945
category of uric acid	0.5820525	1	0.44550893
GLOBAL	18.0768364	12	0.11337734

Figure 3: Scaled Schoenfeld residuals plotted against time for each predictor included in the Cox proportional hazards model.



5.7. Relapse Predictors, Characteristics, Post-Relapse Treatment, and Follow-Up

In this cohort, 14.3% of patients experienced relapse, with 81% of the cohort being male. Among the relapsed patients, 57.9% were classified as high-risk at initial presentation. Relapses occurred predominantly within the first 18 months following initial treatment (63.2%). The most common presenting symptoms at relapse were fever (26.3%), headache (18.4%), and bleeding (13.2%), with the bone marrow (36.8%) and CNS (34.2%) being the most frequently involved sites. At relapse, 38 patients had a WBC of

32,045 ± 98,628/μL, hemoglobin 9.07 ± 10.41 g/dL, platelets 71,095 ± 73,506/μL, LDH 527.5 ± 660.2 U/L, and uric acid 5.00 ± 3.16 mg/dL, reflecting marked laboratory heterogeneity. Treatment for relapse was predominantly with curative intent (68.4%), most often involving chemotherapy alone (76.3%), while a smaller proportion received combined chemoradiation (13.2%). Post-relapse outcomes indicated that 52.6% of patients achieved a second remission, whereas 28.9% died during treatment, resulting in an overall post-relapse mortality of 52.6%. These findings highlight that relapse occurs early, commonly affects the bone marrow and CNS, and carries a substantial risk of mortality despite intensive therapy.

Table 9: Relapse Characteristics, Post-Relapse Treatment of pediatric ALL patients treated at TASH from 2020-2025

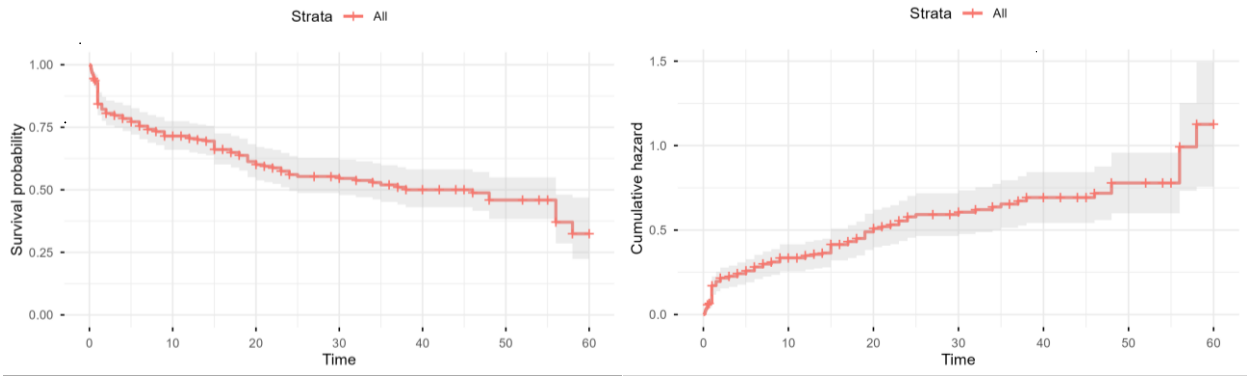
Variable	Category	Count	Percentage
Relapse occurred	No	215	85.7%
	Yes	38	14.3%
Sex	Male	31	81.6%
	Female	7	18.4%
Risk status at diagnosis initial	High risk	22	57.9%
	Standard risk	16	42.1%
Time of relapse	<18 months	24	63.2%
	18-36 months	7	18.4%
	>36 months	7	18.4%
Presenting symptom	Fever	10	26.3%
	Headache	7	18.4%
	Bleeding	5	13.2%
	Headache + Blurred Vision	4	10.5%
	Change in Mentation	4	10.5%
	Visual Difficulty	3	7.9%
	Easy Fatigability	3	7.9%
	Chest Pain	1	2.6%
	Testicular Swelling	1	2.6%

Variable	Category	Count	Percentage
Site of relapse	Bone Marrow	14	36.8%
	CNS	13	34.2%
	Testicular	1	2.6%
	Combined CNS + Bone Marrow	8	21.1%
	Combined Testicular + Bone Marrow	1	2.6%
	Combined CNS + Bone Marrow + Testicular	1	2.6%
Intent of treatment	Curative	26	68.4%
	Palliative	12	31.6%
Therapy after relapse	Chemotherapy	29	76.3%
	Chemotherapy + Radiation	5	13.2%
	Supportive	3	7.9%
	Sent Abroad	1	2.6%
Current status	Alive	17	44.7%
	Dead	20	52.6%

5.7.1. Time-to-Event Analysis for relapse-free survival

Relapse-free Survival in the cohort of 251 patients showed an early decline in the first few months, 74.1 % by month 7. A gradual decline continued throughout follow-up, with relapse-free survival reaching 66.1% by month 15 and 55.3% by month 26. The later months showed a slower but steady reduction, with survival decreasing to 50.0% by month 40 and stabilizing at 45.9% by month 48 onward. A sharp decline was noted after 55 months, reflecting very small cohorts remaining in the study under our observation.

Figure 4: Time-to-Event Analysis of relapse: Kaplan–Meier Survival and Cumulative hazard curves of pediatric ALL patients treated at TASH from 2020-2025



5.7.2. Predictors of time to relapse

In the BI-variable Cox proportional hazards analysis, several variables, including sex, nutritional status at diagnosis, WBC count, mediastinal mass, uric acid level, and prednisolone response, had a p-value <0.25 and were included in the multivariable Cox proportional hazards model. After adjusting for potential confounders, the multivariable model identified elevated WBC count at diagnosis as an independent predictor of hazard.

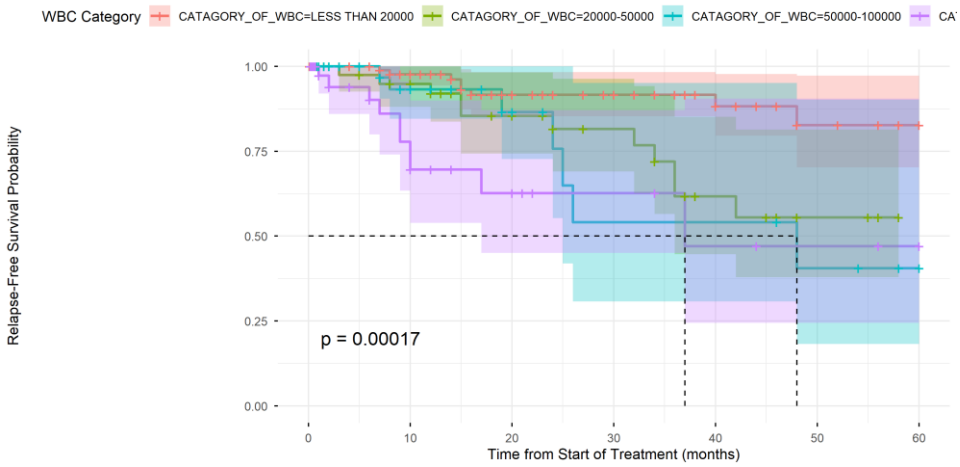
Patients with WBC counts >100,000 had a 7.47-fold higher risk of relapse compared to patients with WBC counts <20,000 (AHR: 7.469; 95% CI: 2.570–21.710; p = 0.0002). Similarly, patients with WBC 20,000–50,000 had a 2.99-fold higher hazard compared to the reference group (AHR: 2.992; 95% CI: 1.186–7.548; p = 0.0203).

Table 10: Bi-variable and Multivariable Cox proportional hazard Model of relapse for patients on treatment of pediatric ALL patients treated at TASH from 2020-2025

Variables	Category	CHR (95% CI)	P value	AHR (95% CI)	P value
Sex	Male (ref)	1	–	1	–
	Female	0.38 (0.17–0.87)	0.022	0.52 (0.22–1.25)	0.143
Nutritional status at diagnosis	Normal (ref)	1	–	1	–
	MAM	1.37 (0.69–2.72)	0.373	0.83 (0.39–1.79)	0.639
	SAM	0.27 (0.04–1.97)	0.195	0.22 (0.03–1.67)	0.143
Risk status at diagnosis	Standard risk (ref)	1	–	–	–
	High risk	2.98 (1.53–5.82)	0.001	3.10 (1.24–7.70)	0.07
Mediastinal mass	No (ref)	1	–	1	–
	Yes	0.38 (0.13–1.08)	0.069	0.56 (0.18–1.77)	0.322
WBC category ($\times 10^3/\mu L$)	<20	1	–	1	–
	20–50	3.10 (1.24–7.70)	0.015	2.79 (1.11–6.99)	0.029
	50–100	3.44 (1.24–9.53)	0.018	3.52 (1.24–9.99)	0.018
	>100	6.91 (2.71–17.61)	<0.001	7.02 (2.53–19.47)	0.0002
Hemoglobin category (g/dL)	<7 (ref)	1	–	–	–
	7–10	0.42 (0.21–0.85)	0.015	–	–
	10–12	Inf	–	–	–
	>12	Inf	–	–	–
Uric acid	<8 (ref)	1	–	1	–
	>8	0.53 (0.21–1.36)	0.186	0.42 (0.16–1.15)	0.091
Prednisolone response	Good (ref)	1	–	–	–
	Poor	5.43 (1.27–23.29)	0.023	–	–

Variables	Category	CHR (95% CI)	P value	AHR (95% CI)	P value
	Not done	1.58 (0.69–3.63)	0.283	–	–
Bone marrow at the end of induction	M1 (ref)	1	–	–	–
	M2	inf	–	–	–

Figure 5: Kaplan–Meier survival curves for relapse by WBC count category of pediatric ALL patients treated at TASH from 2020-2025



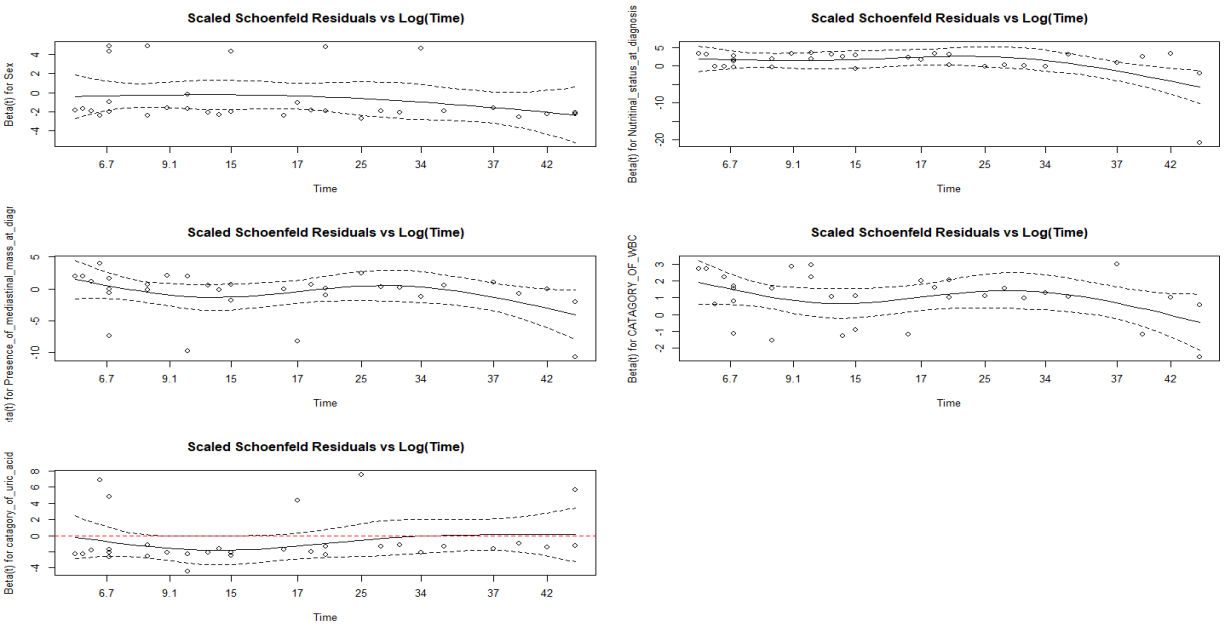
5.7.3. Test of proportional hazard assumption

The proportional hazards assumption of the Cox model was assessed using Schoenfeld residuals. All covariates satisfied the assumption ($p > 0.05$), and the global test was non-significant ($p = 0.138$), indicating no violation. Graphical assessment of scaled Schoenfeld residuals against log time also supported proportionality. These results suggest that the Cox model fits the data well, and hazard ratios can be interpreted reliably over time.

Table 11: Proportional hazard assumption checking using Schoenfeld residual

Variable	Chi-square	Degree of Freedom	p-value
Sex	1.653	1	0.199
Nutritional status at diagnosis	3.338	2	0.188
Presence of mediastinal mass at diagnosis	3.110	1	0.078
WBC category	3.503	3	0.320
Uric acid >8	0.655	1	0.418
GLOBAL	12.313	8	0.138

Figure 6 : Scaled Schoenfeld residuals plotted against time for each predictor included in the Cox proportional hazards model.

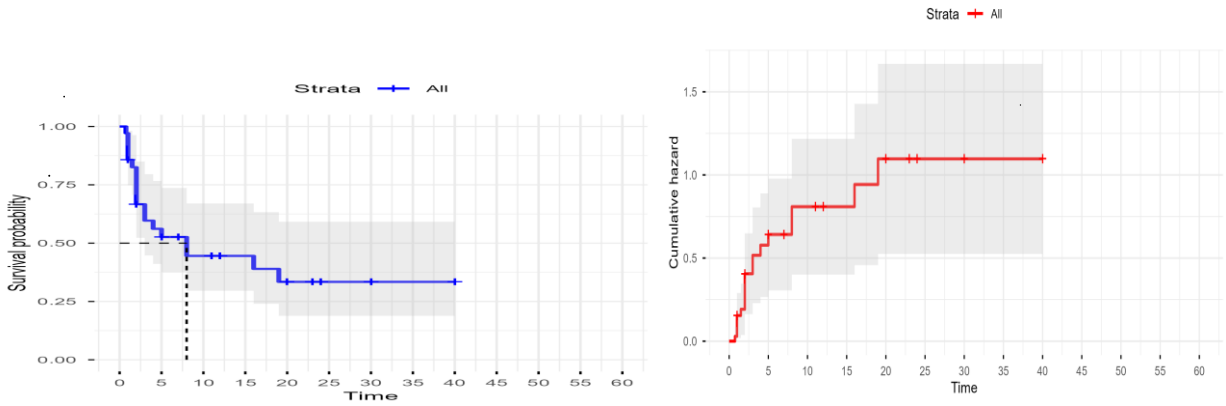


5.8. Post relapse follow-up and survival

In this cohort of 35 patients, 52.6% of the patients died. survival declined most sharply during the first 8 months, dropping from 100% at baseline to 44.5% by month 8, reflecting

the highest-risk period early in follow-up. Additional events reduced survival to 33.4% by month 19, after which it remained stable through month 40. Overall, about one-third of patients survived to the end of follow-up, with the early months representing the critical period for mortality.

Figure 7: Time-to-Event Analysis of post-relapse death: Kaplan–Meier Survival and Cumulative hazard curves



6. Discussion

The age distribution in this cohort (mean 6.24 years; majority aged 1–10 years) matches global ALL patterns. Similar early-childhood peaks are reported in low-income settings such as Ethiopia, Uganda, and India(35)(60)(61)as well as high-income regions, including the COG and European registry studies (62) (3).The male predominance (60.6%; ~1.5:1) is also consistent with reports from sub-Saharan Africa, South Asia, and the Middle East(60) (63)(64) and with SEER and COG data showing persistent male excess across pediatric age groups(9) (65)These findings indicate that the demographic profile of childhood ALL is similar across both low- and high-income countries.

In this cohort, the mean duration of symptoms before diagnosis was 5.67 weeks (SD 5.28), with 29.5% of children experiencing symptoms for more than six weeks. Prolonged symptom duration is common in low-income countries due to delayed recognition, long travel distances, socioeconomic barriers, and reliance on traditional healers(19) (66). (67)In contrast, high-income countries report shorter symptom durations, typically 2–4 weeks, facilitated by better access to primary care and systematic referral, which contributes to lower tumor burden and improved outcomes (9)(3). Symptom duration in LMICs likely contributes to the high frequency of hepatosplenomegaly, lymphadenopathy, and systemic manifestations at presentation, highlighting the need for early diagnosis interventions to improve survival.

Baseline diagnostic findings in our cohort revealed that many children presented with high leukocyte counts, anemia, thrombocytopenia, and varying degrees of tumor burden. Several children also presented with hyperleukocytosis, which is known to increase the risk of early mortality, tumor lysis syndrome, and later relapse. These findings are consistent with sub-Saharan studies, which document delayed health-seeking, lack of early referral systems, and low community awareness, all contributing to advanced disease at presentation(24)(21). In Gondar and Addis Ababa cohorts, more than half of children presented with significant tumor burden anemia, thrombocytopenia, leukocytosis, and liver/spleen enlargement, all associated with poorer early outcomes (68) (69) Similarly, African and Asian LMIC studies report that late presentation with high

tumor burden is typical, largely attributable to socioeconomic barriers, limited diagnostic infrastructure, or misdiagnosis at the primary care level(70)(71)

In our cohort, 81.7% of children with acute lymphoblastic leukemia (ALL) had no tumor lysis syndrome (TLS) at presentation. LMIC studies report higher TLS incidence, with rates ranging from 11–62.6% in pediatric hematologic malignancies, including a Pakistani ALL cohort reporting 62.6% TLS, with a proportion occurring spontaneously. Common biochemical abnormalities included hyperuricemia and hyperphosphatemia, and differences in TLS definitions and monitoring contribute to variability (72) (73) In contrast, HIC data, such as the Chinese Children's Cancer Group (CCCG), reported TLS in 1.4% of 5537 pediatric ALL patients.(74)The lower incidence in our cohort may reflect underestimation due to incomplete work-up, limited laboratory follow-up, and variable timing of TLS assessment.

In our cohort, 92.8% of children were classified as CNS1 at diagnosis, indicating no detectable CNS leukemia. Most studies report CNS involvement at diagnosis as <5% (13); however, CNS2 can be seen in 13–20% after protocol changes [3]. Conventional CSF cytospin may underestimate low-level CNS disease, while more sensitive methods, such as CSF flow cytometry, detect occult blasts in patients initially classified as CNS1(75) (76). These data suggest that the high CNS1 proportion in our cohort may reflect true absence of disease or under-detection due to limitations of cytospin and differences in assessment protocols. The rate of traumatic taps is comparable with other studies, both in LMIC and HIC countries, ranging from 5-20%(59)(13)

At diagnosis, 52.2% of children were classified as standard-risk and 47.4% as high-risk according to NCI criteria, mainly on age, CNS status, and initial white blood cell count, without cytogenetics or immunophenotyping. This distribution aligns with many pediatric ALL cohorts, though LMIC studies often report a higher proportion of high-risk patients due to delayed presentation and higher tumor burden. Clinical NCI risk stratification remains useful for guiding therapy intensity where advanced diagnostics are limited(3) (77)(9)(13)

Early treatment response was generally favorable, with 80.1% had good prednisolone response and 76.1% achieving M1 marrow at the end of induction. While this aligns with

many pediatric ALL cohorts (13)(5)some LMIC studies report lower M1 rates (60–65%) due to delayed diagnosis, higher tumor burden, or treatment interruptions (78) highlighting the impact of healthcare and socioeconomic factors on early outcomes.

Treatment interruptions were documented in 31.9% of patients, while these rates are consistent with LMIC reports highlighting infection and limited supportive care as major contributors(10)(76) some studies, particularly from high-income countries, report significantly lower interruption rates (<15%) due to better infection control, prophylactic measures, and resource availability (3)(9)These discrepancies underscore the influence of healthcare infrastructure and supportive care on uninterrupted therapy and overall outcomes.

In this cohort, mortality was high at 35.2%, with severe infection responsible for 46.2% of deaths, consistent with LMIC reports where infection remains the dominant cause of treatment-related mortality due to limited supportive care and high infectious burden [1,2]. Intracranial hemorrhage accounted for 15.4% of deaths, and leukostatic lung injury and pulmonary hemorrhage were less frequent, patterns similarly described in other resource-limited settings(79)(80) Additionally, 32% of deaths had unknown causes because they occurred at home or in external facilities without diagnostic confirmation, reflecting well-documented gaps in emergency access, referral pathways, and continuity of care in LMIC pediatric oncology systems (62). Importantly, mortality occurred early, with the highest proportion during induction (30.8%), mirroring LMIC findings of elevated early death rates during intensive initial therapy, in contrast to high-income countries where induction mortality is generally <2% owing to superior supportive care, infection control, and rapid critical care access (13)(81)Multiple Ethiopian and regional studies have emphasized sepsis and supportive-care shortfalls (limited blood products, antibiotic availability, ICU beds) as central contributors to early mortality(35) (69)(68)(24).

Overall survival (OS) in our cohort demonstrated 1-year OS was 74.9% and 4-year OS was 54.5%. Other Ethiopian studies similarly report poor long-term outcomes. A Prior study at TASH, including 164 patients, showed an OS at 1, 3, and 5 years was 79 %, 62 %, and 55 % respectively, indicating no major changes in OS in the past 5 years(82). Gondar's study showed 5-year OS ~21%, (24)Jimma University reported a 3-year OS

~39%, with frequent abandonment and low treatment completion.(17) These patterns mirror outcomes across sub-Saharan Africa, where 3–5-year OS often remains below 50%(83) (84)and in LMICs such as Pakistan (5-year OS 52.9%)(84) and Indonesia (3–5-year OS 20–60%)(85)By contrast, high-income countries report markedly higher survival, with Sweden >90% and EUROCARE-5 European cohorts >85% at 5 years(86)(87). These disparities underscore the importance of standardized protocols, adequate supportive care, early diagnosis, and measures to prevent treatment abandonment. Strengthening pediatric oncology infrastructure, improving adherence, and ensuring follow-up are crucial to improving long-term survival in Ethiopia.

After multivariable adjustment, infancy was the strongest predictor of mortality, with infants showing markedly higher adjusted hazard ratios for death than older children. This is consistent with extensive evidence that infant ALL carries uniquely aggressive biology, most notably the high frequency of KMT2A/MLL rearrangements, hyperleukocytosis, and poor chemotherapy tolerance, leading to significantly worse outcomes in both high-income and LMIC settings. (88) (89)(35)(69)(90)(34) confirming the external validity of our observation. Treatment abandonment occurred in 11.2% of our cohort and independently predicted mortality (AHR ≈ 2.4). This finding is consistent with extensive LMIC literature showing that abandonment is among the leading, and importantly modifiable, causes of childhood cancer mortality(91)(92) (21)(93)Systematic reviews and multi-country studies emphasize that abandonment rates in sub-Saharan Africa and South/Southeast Asia range widely often 10–40% or higher depending on setting and tumor type, with social determinants—poverty, long travel distances, caregiver unemployment, cultural or religious preferences, and perception of poor prognosis being principal drivers (94) Ethiopian work has repeatedly documented similar reasons for abandonment (financial hardship, travel burden, use of traditional or religious healing, and family factors) and has linked abandonment to striking reductions in survival (35) (68)Our distribution of reasons including financial issues, opting for religious healing, family issues, community unrest matches these prior reports, underlining that abandonment is not only a medical issue but a social one.

In this cohort, 14.3% of patients experienced relapse. This rate is comparable to or slightly lower than many LMIC reports, where relapse rates range from 15–25% due to delayed diagnosis, treatment interruptions, and limited supportive care (76).(10) In contrast, high-income countries generally report lower relapse rates of 10–15%, reflecting timely diagnosis, intensive risk-adapted therapy, and robust supportive care systems(81) (13). In a previous study in the same center commencing in 2019 showed a relapse rate of 21.4 implying an improved relapse rate in the two cohorts. A similar study in northern Ethiopia showed a relapse rate of 10.1% both cohorts have not described associated predictors for relapse (82) (29),(35). Relapses in our cohort were most common within 18 months, and bone marrow and CNS were the predominant sites, again mirroring LMIC patterns. Post-relapse survival was poor; more than half of the relapsed patients died on follow-up. These outcomes align with reports from other LMICs where salvage options are restricted, and HSCT capacity is limited or absent; relapse is therefore frequently fatal. Studies that show better post-relapse survival typically come from centers with access to advanced salvage regimens, targeted agents, and HSCT resources commonly unavailable in many LMIC settings (95)(23)(96) (97)

We found that WBC at diagnosis was the only variable that independently predicted relapse risk in multivariable analysis: children with WBC >100,000/μL had dramatically higher relapse hazard (AHR ≈ 7.0) compared with those with WBC <20,000/μL, and even moderately elevated WBC (50,000–100,000/μL) showed increased relapse risk (AHR=3.5). This association has strong biologic plausibility—elevated WBC reflects higher disease burden, a greater risk of sanctuary disease (CNS/testes), and a higher probability of minimal residual disease (MRD) persistence when MRD monitoring is not widely available—and is consistently reported in LMIC and HIC literature. In LMIC cohorts lacking comprehensive MRD capabilities, baseline leukocyte count often remains among the most reliable early prognostic markers. Comparative LMIC evidence: multiple studies from South Asia (India, Pakistan, Nepal), Southeast Asia (Indonesia), North Africa (Egypt), and Africa (Kenya, Tanzania) have demonstrated that hyperleukocytosis at diagnosis is associated with increased relapse and inferior event-free survival. For

example, Indian and Pakistani center reports show that children with very high initial WBC counts are likelier to relapse early and to have lower salvage rates post-relapse, largely because of limits in access to intensive salvage regimens and HSCT (95) (23)(70)(96). In Ethiopia and neighboring African cohorts, relapse rates are comparable. Elevated WBC has also been repeatedly associated with induction complications, tumor lysis, (82) (29),(35) .Our findings accord with this evidence base.

7. Strengths and limitations

A major strength of this study is the use of a sizable single-center cohort with comprehensive clinical, laboratory, treatment, and survival information, which allowed for robust survival analyses and multivariable modeling. The application of appropriate statistical methods, including Cox proportional hazards modeling with formal diagnostics to assess proportionality, further strengthens the validity of our findings. Additionally, the uniformity of care pathways within a single institution minimizes variability in treatment practices, enhancing internal consistency.

However, the study also has important limitations. As a retrospective review, it was inherently affected by incomplete documentation and missing data, which may have influenced the precision of some estimates. Furthermore, limitations in diagnostic capacity, including incomplete baseline evaluations and tests such as immunophenotyping and cytogenetic testing, restricted optimal risk stratification and prevented comparison with internationally established risk-based treatment protocols. These constraints reflect broader resource limitations common in many low- and middle-income countries and underscore the need for improved diagnostic infrastructure to enhance care and research accuracy.

8. Recommendations

Based on the findings of this study, several targeted interventions are recommended to improve treatment outcomes for children with acute lymphoblastic leukemia in Ethiopia and comparable low- and middle-income countries.

8.1. Strengthening Early Diagnosis and Referral Systems

Early diagnosis is critical to reducing disease burden at presentation and improving survival. Community-based and primary healthcare training programs should be implemented to enhance early recognition of childhood leukemia symptoms. In addition, streamlined and clearly defined referral pathways from rural and peripheral health facilities to specialized pediatric oncology centers should be established to minimize diagnostic delays and prevent presentation with advanced disease.

8.2. Improving Diagnostic Capacity for Risk Stratification

Accurate risk stratification is essential for optimizing treatment intensity and reducing relapse. Expansion of access to key diagnostic modalities, including immunophenotyping, cytogenetic analysis, and minimal residual disease testing, should be prioritized. Strengthening laboratory quality assurance systems and ensuring completion of baseline diagnostic evaluations for all suspected ALL cases are necessary to support consistent and reliable diagnosis.

8.3. Strengthening Supportive Care Infrastructure

Enhancing supportive care services is vital for reducing treatment-related mortality, particularly during intensive phases such as induction. Consistent availability of broad-spectrum antibiotics, antifungal agents, blood products, and electrolyte monitoring tools should be ensured. Infection prevention strategies, including dedicated isolation facilities, adequately trained nursing staff, and standardized sepsis management protocols, should be reinforced across pediatric oncology units.

8.4. Developing Strategies to Reduce Treatment Abandonment

Treatment abandonment remains a major barrier to cure in resource-limited settings. Targeted psychosocial and financial support programs should be implemented for families at high risk of discontinuing therapy. Improved access to accommodation, transportation

support, and structured counseling services may mitigate socioeconomic and logistical challenges. Engagement of community and religious leaders is also recommended to address misconceptions about cancer treatment and to promote trust in medical care.

8.5. Enhancing Relapse Management Capacity

Strengthening relapse management is essential to improving long-term survival. Standardized salvage chemotherapy protocols and early relapse detection strategies should be introduced. Clear referral pathways to centers with hematopoietic stem cell transplantation capacity should be established, and regional or international collaborations should be expanded to improve access to transplantation for eligible patients.

8.6. Strengthening Data Systems and Long-Term Follow-Up

Robust data systems are necessary for monitoring outcomes and guiding policy decisions. Development and strengthening of pediatric cancer registries and electronic medical record systems should be encouraged to improve data completeness and quality. Additionally, structured long-term follow-up programs should be implemented to facilitate early relapse detection and management of late treatment-related complications.

8.7. Policy Engagement and Resource Mobilization

Sustained improvements in pediatric ALL outcomes require strong policy support. Advocacy efforts should be directed toward increasing national budget allocation for pediatric oncology medications, diagnostics, and supportive care services. Partnerships with international pediatric oncology networks should be fostered to support workforce training, infrastructure development, and procurement of essential supplies.

9. Conclusion

In this cohort of Ethiopian children with acute lymphoblastic leukemia, early mortality, relapse, and treatment abandonment remain major challenges to achieving optimal survival outcomes. Infant age and treatment abandonment emerged as the strongest independent predictors of mortality, underscoring the vulnerability of very young children and the substantial impact of social and economic barriers on treatment completion. Elevated leukocyte count at diagnosis was the only independent predictor of relapse, highlighting the ongoing reliance on clinical and hematologic parameters for risk stratification in settings where advanced diagnostics such as cytogenetics and MRD testing are limited.

The high burden of advanced disease at presentation, coupled with constrained supportive care and limited salvage options, mirrors patterns reported across many low- and middle-income countries. Despite these challenges, the study demonstrates that improved survival is attainable with strengthened early diagnosis, comprehensive supportive care, reduction of treatment abandonment, and enhanced diagnostic capacity.

Overall, the findings emphasize the urgent need for coordinated health-system interventions, investment in diagnostic infrastructure, and patient-centered support programs to improve treatment outcomes for children with ALL in Ethiopia and similar resource-limited settings. Continued efforts to address both medical and socioeconomic barriers are essential to narrowing the survival gap between LMICs and high-income countries.

10. References

1. Pui CH, Yang JJ, Hunger SP, Pieters R, Schrappe M, Biondi A, et al. Childhood acute lymphoblastic leukemia: Progress through collaboration. Vol. 33, Journal of Clinical Oncology. American Society of Clinical Oncology; 2015. p. 2938–48.
2. Malard F, Mohty M. Acute lymphoblastic leukaemia. Vol. 395, The Lancet. Lancet Publishing Group; 2020. p. 1146–62.
3. Inaba H, Greaves M, Mullighan CG. Acute lymphoblastic leukaemia. Vol. 381, The Lancet. Elsevier B.V.; 2013. p. 1943–55.
4. Maloney KW, Devidas M, Wang C, Mattano LA, Friedmann AM, Buckley P, et al. Outcome in Children With Standard-Risk B-Cell Acute Lymphoblastic Leukemia: Results of Children's Oncology Group Trial AALL0331 [Internet]. Vol. 38, J Clin Oncol. 2019. Available from: https://doi.org/10.
5. David T. Teachey, Stephen P. Hunger. Predicting relapse risk in childhood acute lymphoblastic leukaemia [Internet]. [cited 2025 Sep 15]. Available from: https://sci-hub.se/https://doi.org/10.1111/bjh.12442
6. Abboud MR, Ghanem K, Muwakkit S. Acute lymphoblastic leukemia in low and middleincome countries: Disease characteristics and treatment results. Vol. 26, Current Opinion in Oncology. Lippincott Williams and Wilkins; 2014. p. 650–5.
7. Teachey DT, Hunger SP. Predicting relapse risk in childhood acute lymphoblastic leukaemia. Br J Haematol. 2013 Sep;162(5):606–20.
8. Raetz EA, Bhatla T. Where do we stand in the treatment of relapsed acute lymphoblastic leukemia?
9. Hunger & Mullighan. Childhood Cancer by Site Incidence, Survival and Mortality. 2015;
10. Allemani C, Weir HK, Carreira H, Harewood R, Spika D, Wang XS, et al. Global surveillance of cancer survival 1995–2009: analysis of individual data for 25 676 887 patients from 279 population-based registries in 67 countries

(CONCORD-2). The Lancet [Internet]. 2015 Mar 14 [cited 2025 Nov 13];385(9972):977–1010. Available from: https://www.sciencedirect.com/science/article/pii/S0140673614620389?ref=pdf_download&fr=RR-2&rr=99defb4cd9bc7893

11. Ward ZJ, Yeh JM, Bhakta N, Frazier AL, Atun R. Estimating the total incidence of global childhood cancer: a simulation-based analysis. Lancet Oncol [Internet]. 2019 Apr 1 [cited 2025 Sep 18];20(4):483–93. Available from: https://www.sciencedirect.com/science/article/abs/pii/S1470204518309094

12. Monika L Metzger SCHLCFAPRSMLHZZCHPJWRCR. Outcome of childhood acute lymphoblastic leukaemia in resource- poor countries [Internet]. 2003. Available from: www.thelancet.com

13. Raul C. Ribeiro MD, and CHPMD. ribeiro2005. 2005;

14. Kevin C. Oeffinger MD, ACMPhD, CASMD, TKMS, MMHMD, ATMMD. chronic conditions in adult survivors of childhood cancer [Internet]. 2006. Available from: www.nejm.org

15. Hoffman MA, Lent RW, Raque-Bogdan TL. A social cognitive perspective on coping with cancer: Theory, research, and intervention. Counseling Psychologist. 2013 Feb;41(2):240–67.

16. Maurice-Stam H, Oort FJ, Last BF, Brons PPT, Caron HN, Grootenhuis MA. Longitudinal assessment of health-related quality of life in preschool children with non-CNS cancer after the end of successful treatment. Pediatr Blood Cancer [Internet]. 2008 May [cited 2025 Sep 18];50(5):1047–51. Available from: https://pubmed.ncbi.nlm.nih.gov/17914734/

17. Hordofa DF, Ahmed M, Birhanu Z, Weitzman S, Broas J, Shad A, et al. Childhood cancer presentation and initial outcomes in Ethiopia: Findings from a recently opened pediatric oncology unit. PLOS Global Public Health [Internet]. 2024 Jul 10 [cited 2025 Sep 18];4(7):e0003379. Available from:

https://journals.plos.org/globalpublichealth/article?id=10.1371/journal.pgph.0003379

18. Belay A, Ali A, Ayele W, Assefa M, Jemal A, Kantelhardt EJ. Incidence and pattern of childhood cancer in Addis Ababa, Ethiopia (2012–2017). BMC Cancer. 2023 Dec 1;23(1).

19. Abate D, Aman MA, Nasir BB, Gebremariam GT, Fentie AM. Assessment of quality of care using information on patient satisfaction at adult oncology center of Tikur Anbessa specialized hospital, Ethiopia: A cross-sectional study. Patient Prefer Adherence. 2020;14:847–58.

20. Berry DA, Zhou S, Higley H, Mukundan L, Fu S, Reaman GH, et al. Association of minimal residual disease with clinical outcome in pediatric and adult acute lymphoblastic leukemia: A meta-analysis. JAMA Oncol. 2017 Jul 1;3(7).

21. Mirutse MK, Tolla MT, Memirie ST, Palm MT, Hailu D, Abdi KA, et al. The magnitude and perceived reasons for childhood cancer treatment abandonment in Ethiopia: from health care providers' perspective. BMC Health Serv Res. 2022 Dec 1;22(1).

22. Timotewos G, Solomon A, Mathewos A, Addissie A, Bogale S, Wondemagegnehu T, et al. First data from a population based cancer registry in Ethiopia. Cancer Epidemiol. 2018 Apr 1;53:93–8.

23. Siddiqui E, Ghazala Kazi S, Irfan Habib M, Mehmood Ahmed Khan K, Zia N. Pattern of relapse in paediatric acute lymphoblastic leukaemia in a tertiary care unit [Internet]. Vol. 66, Journal of Pakistan Medical Association. 2016. Available from: https://ecommons.aku.edu/pakistan_fhs_mc_emerg_med/131

24. Kassa E, Ayalew M, Birhan M, Gelaw A, Gidey AM, Zeleke TA, et al. Clinical profile and treatment outcomes of acute lymphoblastic leukemia among children attending at the University of Gondar comprehensive specialized hospital and Tikur Anbessa Specialized Hospital in Ethiopia. PLoS One [Internet]. 2025 Jun 1

[cited 2025 Sep 24];20(6):e0322747. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC12140193/

25. Irving JAE, Enshaei A, Parker CA, Sutton R, Kuiper RP, Erhorn A, et al. Integration of genetic and clinical risk factors improves prognostication in relapsed childhood B-cell precursor acute lymphoblastic leukemia. Blood [Internet]. 2016 Aug 18 [cited 2025 Sep 18];128(7):911–22. Available from: https://dx.doi.org/10.1182/blood-2016-03-704973

26. Albaqami WF, Alshamrani AA, Almubarak AA, Alotaibi FE, Alotaibi BJ, Alanazi AM, et al. Genetic and Epigenetic Biomarkers Associated with Early Relapse in Pediatric Acute Lymphoblastic Leukemia: A Focused Bioinformatics Study on DNA-Repair Genes. Biomedicines [Internet]. 2024 Aug 5;12(8):1766. Available from: https://www.mdpi.com/2227-9059/12/8/1766

27. Arega G, Hailu D. 710-TREATMENT OUTCOMES OF ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) AND MAGNITUDE OF ALL RELAPSE IN CHILDREN TREATED AT TIKUR ANBESSA SPECIALIZED HOSPITAL (TASH), ETHIOPIA (A022) Topic. Available from: https://www.researchgate.net/publication/375689495

28. Kassa E, Ayalew M, Birhan M, Gelaw A, Gidey AM, Zeleke TA, et al. Clinical profile and treatment outcomes of acute lymphoblastic leukemia among children attending at the University of Gondar comprehensive specialized hospital and Tikur Anbessa Specialized Hospital in Ethiopia. PLoS One. 2025 Jun 1;20(6 JUNE).

29. Kassa E, Ayalew M, Birhan M, Gelaw A, Gidey AM, Zeleke TA, et al. Clinical profile and treatment outcomes of acute lymphoblastic leukemia among children attending at the University of Gondar comprehensive specialized hospital and Tikur Anbessa Specialized Hospital in Ethiopia. Dilnessa T, editor. PLoS One [Internet]. 2025 Jun 5 [cited 2025 Sep 24];20(6):e0322747. Available from: https://dx.plos.org/10.1371/journal.pone.0322747

30. Kassa E, Ayalew M, Birhan M, Gelaw A, Gidey AM, Zeleke TA, et al. Clinical profile and treatment outcomes of acute lymphoblastic leukemia among children

attending at the University of Gondar comprehensive specialized hospital and Tikur Anbessa Specialized Hospital in Ethiopia. PLoS One. 2025 Jun 1;20(6 JUNE).

31. Sidhu J, Gogoi MP, Krishnan S, Saha V. Relapsed Acute Lymphoblastic Leukemia. Indian J Pediatr [Internet]. 2023 Feb 1 [cited 2025 Sep 1];91(2):158. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC10791726/

32. Sidhu J, Gogoi MP, Krishnan S, Saha V. Relapsed Acute Lymphoblastic Leukemia. Indian J Pediatr [Internet]. 2023 Feb 1 [cited 2025 Sep 1];91(2):158. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC10791726/

33. Tallen G, Ratei R, Mann G, Kaspers G, Niggli F, Karachunsky A, et al. Long-term outcome in children with relapsed acute lymphoblastic leukemia after time-point and site-of-relapse stratification and intensified short-course multidrug chemotherapy: Results of trial ALL-REZ BFM 90. Journal of Clinical Oncology. 2010 May 10;28(14):2339–47.

34. Yadav SP, Kalra M, Anjan M, Sachdeva A. Survival outcome in childhood acute lymphoblastic leukemia in India. Pediatr Blood Cancer [Internet]. 2010 Jan [cited 2025 Nov 25];54(1):178. Available from: https://pubmed.ncbi.nlm.nih.gov/19731333/

35. Hailu A, Mekasha A, Hailu D, Fentie AM, Korones DN, Gidey AM. Impact of Delay Prior to Treatment in Ethiopian Children with Acute Lymphoblastic Leukemia. Pediatric Health Med Ther [Internet]. 2023 May [cited 2025 Nov 25];14:147. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC10184856/

36. Lustosa de Sousa DW, de Almeida Ferreira FV, Cavalcante Félix FH, de Oliveira Lopes MV. Acute lymphoblastic leukemia in children and adolescents: prognostic factors and analysis of survival. Rev Bras Hematol Hemoter [Internet]. 2015 Jul 1 [cited 2025 Sep 18];37(4):223–9. Available from: https://www.sciencedirect.com/science/article/pii/S1516848415000547

37. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. CA Cancer J Clin. 2023 Jan;73(1):17–48.

38. Inaba H, Greaves M, Mullighan CG. Acute lymphoblastic leukaemia. Vol. 381, The Lancet. Elsevier B.V.; 2013. p. 1943–55.

39. Smith MA, Seibel NL, Altekruse SF, Ries LAG, Melbert DL, O'Leary M, et al. Outcomes for children and adolescents with cancer: Challenges for the twenty-first century. Journal of Clinical Oncology. 2010 May 20;28(15):2625–34.

40. Metayer C, Dahl G, Wiemels J, Miller M. Childhood Leukemia: A preventable disease. Pediatrics. 2016 Nov 1;138:S45–55.

41. Zhang J, Ding L, Holmfeldt L, Wu G, Heatley SL, Payne-Turner D, et al. The genetic basis of early T-cell precursor acute lymphoblastic leukaemia. Nature [Internet]. 2012 Jan 12 [cited 2025 Sep 15];481(7380):157–63. Available from: https://www.nature.com/articles/nature10725

42. Greaves M. A causal mechanism for childhood acute lymphoblastic leukaemia. Vol. 18, Nature Reviews Cancer. Nature Publishing Group; 2018. p. 471–84.

43. Buffler P, Kwan M, Reynolds P, Urayama K. Environmental and Genetic Risk Factors for Childhood Leukemia: Appraising the Evidence. Cancer Invest. 2005 Feb 1;23(1):60–75.

44. Palladino MM. Reduction in late mortality among 5-year survivors of childhood cancer. Vol. 114, Archivos Argentinos de Pediatria. Sociedad Argentina de Pediatria; 2016. p. e273–4.

45. Magrath I, Steliarova-Foucher E, Epelman S, Ribeiro RC, Harif M, Li CK, et al. Paediatric cancer in low-income and middle-income countries. Lancet Oncol [Internet]. 2013 Mar 1 [cited 2025 Sep 18];14(3):e104–16. Available from: https://www.sciencedirect.com/science/article/abs/pii/S1470204513700081

46. Terwilliger T, Abdul-Hay M. Acute lymphoblastic leukemia: a comprehensive review and 2017 update. Vol. 7, Blood Cancer Journal. Springer Nature; 2017.

47. Teachey DT, Pui CH. Comparative features and outcomes between paediatric T-cell and B-cell acute lymphoblastic leukaemia. Lancet Oncol [Internet]. 2019 Mar 1 [cited 2025 Sep 18];20(3):e142–54. Available from: https://pubmed.ncbi.nlm.nih.gov/30842058/

48. Harrison CJ. Prevention of childhood leukaemia by lifestyle changes. Leukemia [Internet]. 2021 May 1 [cited 2025 Sep 18];35(5):1265–6. Available from: https://pubmed.ncbi.nlm.nih.gov/33833383/

49. Li JF, Ma XJ, Ying LL, Tong YH, Xiang XP. Multi-Omics Analysis of Acute Lymphoblastic Leukemia Identified the Methylation and Expression Differences Between BCP-ALL and T-ALL. Front Cell Dev Biol [Internet]. 2021 Jan 21 [cited 2025 Sep 18];8:622393. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC7859262/

50. Gardie Y, Wassie M, Wodajo S, Giza M, Ayalew M, Sewale Y, et al. Delay in diagnosis and associated factors among children with cancer admitted at pediatric oncology ward, University of Gondar comprehensive specialized hospital, Ethiopia: a retrospective cross-sectional study. BMC Cancer. 2023 Dec 1;23(1).

51. van Weelderen RE, Njuguna F, Klein K, Mostert S, Langat S, Vik TA, et al. Outcomes of pediatric acute myeloid leukemia treatment in Western Kenya. Cancer Rep (Hoboken) [Internet]. 2022 Oct 1 [cited 2025 Sep 18];5(10). Available from: https://pubmed.ncbi.nlm.nih.gov/34811958/

52. International Partnerships Lead to Strides in Pediatric Leukemia in El Salvador. 2021.

53. Executive summary. The Selection and Use of Essential Medicines 2021 Report of the 23 rd WHO Expert Committee on the Selection and Use of Essential Medicines [Internet]. 2021. Available from: http://apps.who.int/bookorders.

54. Mitchell HR, Lu X, Myers RM, Sung L, Balsamo LM, Carroll WL, et al. Prospective, longitudinal assessment of quality of life in children from diagnosis to 3 months off treatment for standard risk acute lymphoblastic leukemia: Results of

Children's Oncology Group study AALL0331. Int J Cancer [Internet]. 2016 Jan 15 [cited 2025 Sep 18];138(2):332–9. Available from: https://pubmed.ncbi.nlm.nih.gov/26235006/

55. Mirutse MK, Tolla MT, Memirie ST, Palm MT, Hailu D, Abdi KA, et al. The magnitude and perceived reasons for childhood cancer treatment abandonment in Ethiopia: from health care providers' perspective. BMC Health Serv Res [Internet]. 2022 Dec 1 [cited 2025 Sep 18];22(1):1–13. Available from: https://bmchealthservres.biomedcentral.com/articles/10.1186/s12913-022-08188-8

56. Sitaresmi MN, Mostert S, Schook RM, Sutaryo, Veerman AJP. Treatment refusal and abandonment in childhood acute lymphoblastic leukemia in Indonesia: an analysis of causes and consequences. Psychooncology [Internet]. 2010 Apr 1 [cited 2025 Sep 18];19(4):361–7. Available from: /doi/pdf/10.1002/pon.1578

57. Solgun HA, Yıldırgan DO, Terzi O, Bayram C. Immunological and cytogenetic features, treatment management and prognosis in pediatric relapsed/refractory leukemias.

58. Barredo JC, Devidas M, Lauer SJ, Billett A, Marymont MA, Pullen J, et al. Isolated CNS relapse of acute lymphoblastic leukemia treated with intensive systemic chemotherapy and delayed CNS radiation: A pediatric oncology group study. Journal of Clinical Oncology. 2006 Jul 1;24(19):3142–9.

59. Masurekar AN, Parker CA, Shanyinde M, Moorman A V., Hancock JP, Sutton R, et al. Outcome of central nervous system relapses in childhood acute lymphoblastic Leukaemia - Prospective open cohort analyses of the ALLR3 trial. Vol. 9, PLoS ONE. Public Library of Science; 2014.

60. Mutyaba I, Wabinga HR, Orem J, Casper C, Phipps W. Presentation and Outcomes of Childhood Cancer Patients at Uganda Cancer Institute. Glob Pediatr Health. 2019;6.

61. Arora RS, Eden T, Kapoor G. Epidemiology of childhood cancer in India. Indian J Cancer [Internet]. 2009 Oct 1 [cited 2025 Dec 3];46(4):264–73. Available from: https://pubmed.ncbi.nlm.nih.gov/19749456/

62. Gupta S, Hunger SP. Recent trends in the results of studies conducted by the Children's Oncology Group acute lymphoblastic leukemia committee and implications for emerging cooperative trial groups in low- and middle-income countries. Pediatric Hematology Oncology Journal. 2020 Oct;5(4):151–5.

63. B T, F T, AK D, P T, H D, B M, et al. Childhood acute lymphoblastic leukemia in sub Saharan Africa: 4 years? experience at the pediatric oncology unit Bamako, Mali. Journal of Child and Adolescent Health. 2018;02(02).

64. Al-Mulla NA, Chandra P, Khattab M, Madanat F, Vossough P, Torfa E, et al. Childhood acute lymphoblastic leukemia in the Middle East and neighboring countries: a prospective multi-institutional international collaborative study (CALLME1) by the Middle East Childhood Cancer Alliance (MECCA). Pediatr Blood Cancer [Internet]. 2014 Aug 1 [cited 2025 Dec 3];61(8):1403–10. Available from: https://pubmed.ncbi.nlm.nih.gov/24648275/

65. Ward E, DeSantis C, Robbins A, Kohler B, Jemal A. Childhood and adolescent cancer statistics, 2014. CA Cancer J Clin [Internet]. 2014 Mar [cited 2025 Dec 3];64(2):83–103. Available from: https://pubmed.ncbi.nlm.nih.gov/24488779/

66. Mutyaba I, Wabinga HR, Orem J, Casper C, Phipps W. Presentation and Outcomes of Childhood Cancer Patients at Uganda Cancer Institute. Glob Pediatr Health. 2019;6.

67. Gizaw AT, Woldie I, Yilma AN, Tadesse M, Sisay AL, Sebero FM, et al. Barriers to timely diagnosis and treatment of childhood cancer in Sub-Sahara Africa: a qualitative systematic review. BMC Cancer [Internet]. 2025 Dec 1 [cited 2025 Dec 3];25(1):1600. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC12534927/

68. Molla YM, Shad A, Wali R, Yimer MA. The magnitude and associated factors of childhood cancer treatment abandonment at the university of Gondar comprehensive specialized hospital, Ethiopia. Sci Rep. 2025 Dec 1;15(1).

69. Sifer SD, Solomon M. Survival Status and Predictors of Mortality Among Children Admitted With Acute Lymphocytic Leukemia at Cancer Treatment Hospitals in Addis Ababa, Ethiopia. Cancer Control [Internet]. 2024 Jan 1 [cited 2025 Nov 25];31:10732748241266508. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC11268005/

70. Ramadhan MH, Sari NM, Peryoga SU, Susanah S. Survival and Treatment Outcomes of Childhood Acute Lymphoblastic Leukemia in a Low-Middle Income Country: A Single-Center Experience in West Java, Indonesia. J Blood Med [Internet]. 2024 [cited 2025 Nov 25];15:77. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC10887884/

71. Gupta S, Howard SC, Hunger SP, Antillon FG, Metzger ML, Israels T, et al. Treating Childhood Cancer in Low- and Middle-Income Countries. Disease Control Priorities, Third Edition (Volume 3): Cancer [Internet]. 2015 Nov 1 [cited 2025 Nov 25];121–46. Available from: https://www.ncbi.nlm.nih.gov/books/NBK343626/

72. Naeem B, Moorani KN, Anjum M, Imam U. Tumor lysis syndrome in pediatric acute lymphoblastic leukemia at tertiary care center: Tumor lysis syndrome in pediatric ALL. Pak J Med Sci [Internet]. 2019 Jul 9 [cited 2025 Dec 3];35(4):899–904. Available from: https://www.pjms.org.pk/index.php/pjms/article/view/715

73. Pei Y, Li Y, Liang Y, Xu L, Huang X, Li Y, et al. Evaluation of the safety and efficacy of low-dose rasburicase in critically ill children with haematological malignancies. Int J Clin Pharm. 2020 Dec 1;42(6):1440–6.

74. Xue Y, Chen J, Gao S, Zhai X, Wang N, Gao J, et al. Clinical characteristics of tumor lysis syndrome in childhood acute lymphoblastic leukemia. Sci Rep [Internet]. 2021 Dec 1 [cited 2025 Dec 3];11(1):9656. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC8102476/

75. Rodriguez A, Wengyn M, Vu MH, Doan A, Raca G, Bhojwani D, et al. Impact of Central Nervous System (CNS) Leukemia Status-Based Therapeutic Protocol Change on the Incidence of CNS2 Diagnosis in Pediatric B-Lymphoblastic Acute Leukemia. Blood [Internet]. 2023 Nov 2 [cited 2025 Dec 3];142(Supplement 1):1457. Available from: https://www.sciencedirect.com/science/article/pii/S0006497123080606

76. Duffy C, Graetz DE, Lopez AMZ, Carrillo AK, Job G, Chen Y, et al. Retrospective analysis of outcomes for pediatric acute lymphoblastic leukemia in South American centers. Front Oncol. 2023 Oct 30;13:1254233.

77. Duffy C, Graetz DE, Lopez AMZ, Carrillo AK, Job G, Chen Y, et al. Retrospective analysis of outcomes for pediatric acute lymphoblastic leukemia in South American centers. Front Oncol. 2023 Oct 30;13:1254233.

78. Duffy C, Graetz DE, Lopez AMZ, Carrillo AK, Job G, Chen Y, et al. Retrospective analysis of outcomes for pediatric acute lymphoblastic leukemia in South American centers. Front Oncol. 2023 Oct 30;13:1254233.

79. Rahat-Ul-Ain, Faizan M, Shamim W. Treatment-related mortality in children with acute lymphoblastic leukaemia in a low-middle income country. J Pak Med Assoc [Internet]. 2021 Oct 1 [cited 2025 Dec 3];71(10):2373–7. Available from: https://pubmed.ncbi.nlm.nih.gov/34974574/

80. Mostert S, Arora RS, Arreola M, Bagai P, Friedrich P, Gupta S, et al. Abandonment of treatment for childhood cancer: position statement of a SIOP PODC Working Group. Lancet Oncol. 2011 Aug;12(8):719–20.

81. Hunger SP, Mullighan CG. Acute Lymphoblastic Leukemia in Children. Longo DL, editor. New England Journal of Medicine [Internet]. 2015 Oct 15 [cited 2025 Dec 3];373(16):1541–52. Available from: https://www.nejm.org/doi/pdf/10.1056/NEJMra1400972

82. (PDF) 710 -TREATMENT OUTCOMES OF ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) AND MAGNITUDE OF ALL RELAPSE IN CHILDREN

TREATED AT TIKUR ANBESSA SPECIALIZED HOSPITAL (TASH), ETHIOPIA (A022) Topic AS05 SIOP Scientific Program Affiliations [Internet]. [cited 2025 Nov 25]. Available from: https://www.researchgate.net/publication/375689495_710_-TREATMENT_OUTCOMES_OF_ACUTE_LYMPHOBLASTIC_LEUKEMIA_ALL_AND_MAGNITUDE_OF_ALL_RELAPSE_IN_CHILDREN_TREATED_AT_TIKUR_ANBESSA_SPECIALIZED_HOSPITAL_TASH_ETHIOPIA_A022_Topic_AS05_SIOP_Scientific_Program

83. Olbara G, van der Wijk T, Njuguna F, Langat S, Mwangi H, Skiles J, et al. Childhood acute lymphoblastic leukemia treatment in an academic hospital in Kenya: Treatment outcomes and health-care providers' perspectives. Pediatr Blood Cancer [Internet]. 2021 Dec 1 [cited 2025 Dec 4];68(12). Available from: https://pubmed.ncbi.nlm.nih.gov/34569156/

84. Borella L, Casper JT, Lauer SJ. Shifts in Expression of Cell Membrane Phenotypes in Childhood Lymphoid Malignancies at Relapse [Internet]. Vol. 54, Blood. Available from: http://ashpublications.org/blood/article-pdf/54/1/64/582566/64.pdf

85. Sitaresmi MN, Mostert S, Gundy CM, Sutaryo, Veerman AJP. Health-related quality of life assessment in Indonesian childhood acute lymphoblastic leukemia. Health Qual Life Outcomes [Internet]. 2008 Nov 9 [cited 2025 Dec 4];6. Available from: https://pubmed.ncbi.nlm.nih.gov/18992169/

86. Björk-Eriksson T, Boström M, Bryngelsson IL, Lähteenmäki PM, Jarfelt M, Kalm M, et al. Mortality Among Pediatric Patients With Acute Lymphoblastic Leukemia in Sweden From 1988 to 2017. JAMA Netw Open [Internet]. 2022 Nov 28 [cited 2025 Dec 4];5(11):E2243857. Available from: https://pubmed.ncbi.nlm.nih.gov/36441552/

87. Gatta G, Botta L, Rossi S, Aareleid T, Bielska-Lasota M, Clavel J, et al. Childhood cancer survival in Europe 1999-2007: results of EUROCARE-5--a population-based study. Lancet Oncol [Internet]. 2014 Jan [cited 2025 Dec 4];15(1):35–47. Available from: https://pubmed.ncbi.nlm.nih.gov/24314616/

88. Bernard J, Weil M, Jacquillat C. Treatment of acute lymphoblastic leukemia. N Engl J Med [Internet]. 2006 [cited 2025 Nov 25];354(2):1–11. Available from: https://pubmed.ncbi.nlm.nih.gov/16407512/

89. Sahoo D, Mohapatra S. Infant acute lymphoblastic leukemia: a view from India. Pediatric Hematology Oncology Journal [Internet]. 2025 Sep 1 [cited 2025 Nov 25];10(3):100467. Available from: https://www.sciencedirect.com/science/article/pii/S246812452500035X

90. Shimizu K, Luhulla K, Msoffe M, Chambega C, Mahawi S, Ewald P, et al. Clinical characteristics and outcomes of paediatric acute lymphoblastic leukaemia in a tertiary hospital in Tanzania: a single-centre observational study. Trop Med Health [Internet]. 2025 Dec 1 [cited 2025 Sep 24];53(1):1–11. Available from: https://tropmedhealth.biomedcentral.com/articles/10.1186/s41182-025-00760-2

91. Stanley CC, van der Gronde T, Westmoreland KD, Salima A, Amuquandoh A, Itimu S, et al. Risk factors and reasons for treatment abandonment among children with lymphoma in Malawi. Support Care Cancer [Internet]. 2018 Mar 1 [cited 2025 Nov 25];26(3):967–73. Available from: https://pubmed.ncbi.nlm.nih.gov/28986643/

92. Yimer M, Fufa D, Njuguna F, Mdoka C, Chagaluka G, Molyneux E, et al. Significant Impact of Treatment Abandonment on Survival of Children With “Common and Curable” GICC Index Cancers in Sub-Saharan Africa-A Multicenter Prospective CANCaRe Africa Study. Pediatr Blood Cancer [Internet]. 2025 Nov 1 [cited 2025 Nov 25];72(11). Available from: https://pubmed.ncbi.nlm.nih.gov/40899378/

93. Atwiine B, Mdoka C, Branchard M, Chagaluka G, Fufa D, Ayalew M, et al. Title: Prevention of treatment abandonment remains an important challenge to increase survival of Wilms tumor in sub-Saharan Africa: A report from Wilms Africa-CANCaRe Africa.

94. Friedrich P, Lam CG, Kaur G, Itriago E, Ribeiro RC, Arora RS. Determinants of Treatment Abandonment in Childhood Cancer: Results from a Global Survey.

PLoS One [Internet]. 2016 Oct 1 [cited 2025 Nov 25];11(10). Available from: https://pubmed.ncbi.nlm.nih.gov/27736871/

95. Kong SG, Seo JH, Jun SE, Lee BK, Lim YT. Childhood acute lymphoblastic leukemia with hyperleukocytosis at presentation. Blood Res [Internet]. 2014 [cited 2025 Nov 25];49(1):29. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC3974953/

96. AlMalki M, Abdulatef M, Altrabolsi H, Shubayr N. Outcomes of children treated for relapsed or refractory acute lymphoblastic leukemia: A single tertiary care center experience. Cancer Rep [Internet]. 2024 Jul 1 [cited 2025 Nov 25];7(7):e2117. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC11270327/

97. Fullmer A, O'Brien S, Kantarjian H, Jabbour E. Novel Therapies for Relapsed Acute Lymphoblastic Leukemia. Curr Hematol Malig Rep [Internet]. 2009 [cited 2025 Nov 25];4(3):148. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC4572835/

Appendix

1.Data Collection Questionaries

Based on the Research Questions and Objectives for the study at Black Lion Specialized Hospital (BLSH), here is an outline of the necessary data points to collect, structured like a data abstraction form or questionnaire for retrospective chart review.

Data Abstraction Form: Predictors of Relapse in Pediatric ALL at TASH (2020-2025)

Instructions: Collect data retrospectively from patient medical records. Use "NR" for "Not Recorded" or "NA" for "Not Applicable". Ensure patient confidentiality is maintained; use study IDs only.

Section A: Patient Identification

1. Study ID: _____
2. Hospital Record Number (MRN): _____ (Use only for data collection linkage, remove/anonymize for analysis)
3. Age (years)_____
4. Sex: □Male □ Female

Section B: Socioeconomic and demographic Factors

1. Estimated Distance from Home to BLSH:

□In Addis Ababa □Less than 100 km from Addis Ababa □100-300 km from Addis Ababa □300-600 km from Addis Ababa □more than 600 km from Addis Ababa

2. Caregivers highest level of education:

□No Formal Education □Primary School (Grades 1-8) □Secondary School (Grades 9-12)□Tertiary (College/University/Vocational)□Unknown

3. Care givers monthly income:

□Less than 4000 birr □ 4000-8000 birr □8000-12000 birr □more than 12000 birr

4. Documented Need for Financial Assistance/Support during treatment?

□Yes (e.g., Social work) □No indication found □ NR

Section C: Clinical Characteristics at initial Diagnosis

1. Duration since diagnosis in months: _____
2. Age at Diagnosis: _____ Years
3. Initial White Blood Cell (WBC) Count at Diagnosis: _____/µL (or x10⁹/L)
4. Initial Hemoglobin at diagnosis_____gm/dl
5. Initial Platelet count at diagnosis_____/microliter
6. Presence of CNS disease at Diagnosis:

□CNS 1 □CNS 2 □CNS 3 □ Image/ Clinical diagnosis

7. Presence of Testicular disease at Diagnosis (Males only):

□Yes (Documented by clinical exam/ultrasound) □No □Not Assessed / NR

□Not Applicable (Female)

6. Splenic involvement at diagnosis □Yes □No
7. Liver involvement at diagnosis □Yes □No
8. Renal involvement at diagnosis □Yes □No
9. Presence of Mediastinal Mass at Diagnosis: □Yes □No

Section D: Biological Factors (Relates to RQ2 & Obj 2)

1. Cytogenetic Analysis Performed? Cytogenetic Results

□Not performed □Hyperdiploidy (>50 chromosomes)

□Hypodiploidy (<44 chromosomes) □t(9;22) [BCR-ABL1]

□t(12;21) [ETV6-RUNX1] □MLL (KMT2A) rearrangement

□Other abnormality (Specify: _____)

2. Immunophenotype:

□B-cell precursor ALL □T-cell ALL (□Ambiguous/Mixed Phenotype)

□Not Determined / Not Recorded

3. Method of Immunophenotyping:

□Flow Cytometry □Immunohistochemistry □Morphology only □Not Specified / NR

Section E: Treatment Details & Related Variables (Relates to RQ4 & Obj 4)

1. Duration since treatment initiated: _____months
2. Treatment Protocol Received:

   □COG adapted protocol □BFM ALL Protocol □Other specify)_____
3. Risk status of patient

   □Standard risk □Intermediate risk □High risk
3. Documented Treatment Interruptions (excluding planned breaks)?

   □ Yes □ No □NR
4. If Yes, Number of Documented Interruptions: _____
5. If Yes, Primary Reason(s) for Interruptions: (Check all that apply)

□Severe Toxicity / Side Effects (e.g., mucositis, organ damage) □Unavailability of Chemotherapy Drugs □patient didn't come for follow up □Refusal to take medication □Not applicable

6. Treatment Abandonment Occurred? □Yes □No
   (Use operational definition: e.g., failure to return for scheduled curative therapy for >[Specify duration, e.g., 4-8 weeks] without medical justification despite contact attempts)
7. Reason for Abandonment (if documented):

□Financial issues □Family issues □Was too far away to come □Opted for traditional or religious medicine □unrest in the □Reason Unknown □Not applicable

Section F: Treatment response

1. Prednisolone response for Pro phase

   □Not done □Prednisolone good response □prednisolone poor response
2. Bone marrow status at the end of induction?

   □M1 □M2 □M3 □Not available

Section G: Characteristics of relapse (Only for relapsed patients)

1. Number of relapses _____

2. Time of first relapse since treatment has been started in months_____

3. Site of First Relapse:

□Bone Marrow □Central Nervous System (CNS)□Testicular □Combined (CNS and bone marrow:) □Combined Testicullar and bone marrow □Other _____

Section H: Treatment of relapse

1, Intent of therapy for relapse □Curative □Palliative

2. Type of therapy after relapse □Chemotherapy □Radiation(Testicular or Craniospinal) □ chemotherapy plus radiotherapy □sent abroad for better therapy

□Referred abroad for better care

3. Out come after treatment

□ Achieved second remission □Failed remission □Died on treatment □Unknown