DOI: https://dx.doi.org/10.4314/ejpch.v19i2.5

Ethiopian Journal of Pediatrics and Child Health, 2024, 19(2)
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ISSN 2413-2640 *eISSN* 2519-0334

OPEN ACCESS

Original article

Delay in treatment for childhood Acute Lymphoblastic Leukemia at the University of Gondar Comprehensive Specialized Hospital, Northwestern Ethiopia

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Abstract

Background: *Despite the critical importance of early blood cancer diagnosis in children for timely treatment, late presentation, delayed diagnosis, and delayed treatment initiation remain significant issues in developing countries, including Ethiopia. Addressing these delays requires improving healthcare infrastructure, public awareness, provider training, and reducing financial barriers. This study aimed to assess referral delays, diagnostic delays, and overall treatment delays among children with acute lymphoblastic leukemia at the University of Gondar Comprehensive Specialized Hospital.*

Citation : Kassa E., Ayalew M., Birhan M., Gelaw A., Giday A. M., Tilahun D., Abebe H., Mekonnen A., Teklehaimanot E., Berhane N., Delay in treatment for childhood acute lymphoblastic leukemia at the University of Gondar Comprehensive Specialized Hospital, Northwestern Ethiopia. *Ethiop J Pediatr Child Health*. 2024;19 (2):133-151 ***Submission date:*** *20 June 2024* ***Accepted****: 23 December 2024* ***Published****: 31 December 2024*

Methods: *A facility-based cross-sectional study was conducted among pediatric acute lymphoblastic leukemia (ALL) patients under 18 years. Data were collected using a structured questionnaire administered to primary caregivers from December 29, 2022, to January 30, 2024. During the study, 90 ALL cases were included using a consecutive sampling technique. Data were entered and analyzed using SPSS version 25 software, with results presented through descriptive statistics, including frequencies, percentages, graphs, and tables. Binary logistic regression examined associations between sociodemographic factors and treatment delays among childhood ALL patients.*

Results: *A total of 90 children participated, 63 (70.0%) male. Median time from first symptoms to medical consultation was 9.7 days, referral delay 51.3 days, diagnosis delay 3.2 days, and treatment initiation delay 4.6 days. Total delay to treatment was 69 days, with induction mortality at 22%. High-risk ALL, malaria, and delays of 30–90 days increased induction mortality risk.*

Conclusion: *The study revealed significant delays in childhood ALL treatment, contributing to high mortality rates. Timely diagnosis and treatment initiation are critical, particularly for high-risk patients and those with malaria. Strengthening healthcare infrastructure, awareness, and provider training is vital to improve outcomes.*

Keywords: *Delay, acute lymphoblastic leukemia, induction mortality, Ethiopia*

Introduction

Cancer is a significant public health, social, and economic threat, particularly in low- and middle-income countries (LMICs). More than 85% of worldwide childhood cancers are diagnosed in LMICs, such as Ethiopia (1). The cure rate for childhood cancer in high-income countries has reached over 90%, but it remains below 20-30% in LMICs (2, 3). Leukemias are one of the most common types of neoplasms among children, accounting for approximately 30% of oncological diagnoses. Among all bone marrow (BM) derived neoplasms, acute lymphoblastic leukemia (ALL) is the most prevalent type, occurring in 80% of patients suffering from leukemias (4). In recent decades, infectious diseases have been a major health burden in developing countries like Ethiopia. Despite this, pediatric cancer death rates in LMICs remain alarmingly high, often nearing 100% (5).

Acute lymphoblastic leukemia (ALL) is a hematological emergency (6). It accounts for more than 26% of all childhood cancers in the U.S. (7) and 30% in Europe and LMICs (8). Globally, the incidence of ALL cases increased by 30.81% between 1990–2017 (8-10). Thiopurines, such as 6-mercaptopurine, are primarily used in the treatment of childhood ALL. However, they can induce severe adverse drug reactions (ADRs), including allergic reactions (25%), hepatotoxicity (34%), bone marrow suppression (7%), myelosuppression, and secondary tumor formation (11). To monitor these

risks, patients are routinely screened for blood cell counts. The pharmacogenetics of thiopurine myelotoxicity is partly explained by genetic variants in the thiopurine methyltransferase (TPMT) gene (12).

The determinants of delayed diagnosis in developing countries vary across studies(13). Factors associated with delay include health insurance, parental attitudes, the health care system, and health personnel (14, 15). Blood cancer patients often experience multiple consultations in primary care before specialist referral, leading to prolonged diagnostic intervals (15). Early diagnosis of childhood malignancies is frequently challenging due to nonspecific symptoms. Delays in diagnosis can prevent timely treatment and cause unnecessary complications. Prolonged diagnostic delays have a negative impact on prognosis (16). The causes of delays can be categorized into three groups: patient delay, doctor delay (referral delay), diagnosis delay, and treatment delay. The definition of delay is often relative (16, 17). Much of the literature defines delays as a gap of more than 30 days between the onset of symptoms and the initiation of treatment, with 30 days often serving as a cutoff point for identifying delays at various stages of care. While there is no consensus on the precise duration that constitutes a delay, studies commonly categorize delays into the following ranges: <30 days, 30-60 days, 61-90 days, 91-120 days, and >120 days (18).

Induction mortality is defined as death occurring within 42 days of initiating induction treatment (17, 18). Delays in referral and diagnosis have been shown to have a potential negative impact on the outcomes of some solid tumors (19). Regardless of the cause of delay, there is evidence that delayed referral to a specialist center or failure to refer at all can negatively impact patient outcomes (20). Understanding the potential factors influencing the delay in cancer diagnosis is crucial to addressing this issue and developing effective strategies for the pediatric population in Ethiopia. This study aimed to investigate magnitude of induction mortality and patterns of referral delays, diagnostic delays, and overall treatment delays among children with ALL attending the University of Gondar Compressive Specialized Hospital.

Methods and Materials

Study setting

This study was conducted at the University of Gondar Comprehensive Specialized Hospital (UoGCSH). It is located in Amhara National Regional State (ANRS), Northwestern Ethiopia. The hospital is 750 km from Addis Ababa, the capital city. As the largest and most comprehensive multidisciplinary specialized hospital in the Central-North Gondar zone, the UoGCSH serves over 7 million people annually within its catchment areas and has 550 beds (21). It offers various health services, including pediatric hematology and oncology. The pediatric hematology-oncology center is the only one of its kind in the ANRS (22, 23). The ward is staffed by one hematologist-oncologist, three pediatrician fellows, 11 BSC

comprehensive nurses, and temporary resident and intern doctors (21).

Study design and period

A cross-sectional study was conducted in an institutional setting to investigate the occurrence of ALL and identify associated delayed factors. The study included both outpatients and inpatients who sought medical care at the UoGCSH between December 29, 2022, and January 30, 2024.

Source and study population

The source population for this study consisted of children under 18 years who visited the pediatric outpatient department (OPD) and those who were admitted to the pediatric oncology unit at the UoGCSH. These children were included in the study if they had clinically suspected ALL and abnormal hematological profiles.

Sample size and sampling technique

A time-delimitated consecutive sampling technique was employed to recruit the study subjects. Given the relatively rare nature of ALL and the institutional setting of the study, we included all available cases during the study period. A total of 90 ALL patients were recruited and participated in the study.

Operational definition and measurements

Patient delay (PD): From the first symptom to the first medical consultation (24)

Diagnostic delay (DD): From the first medical consultation to the time of diagnosis (24).

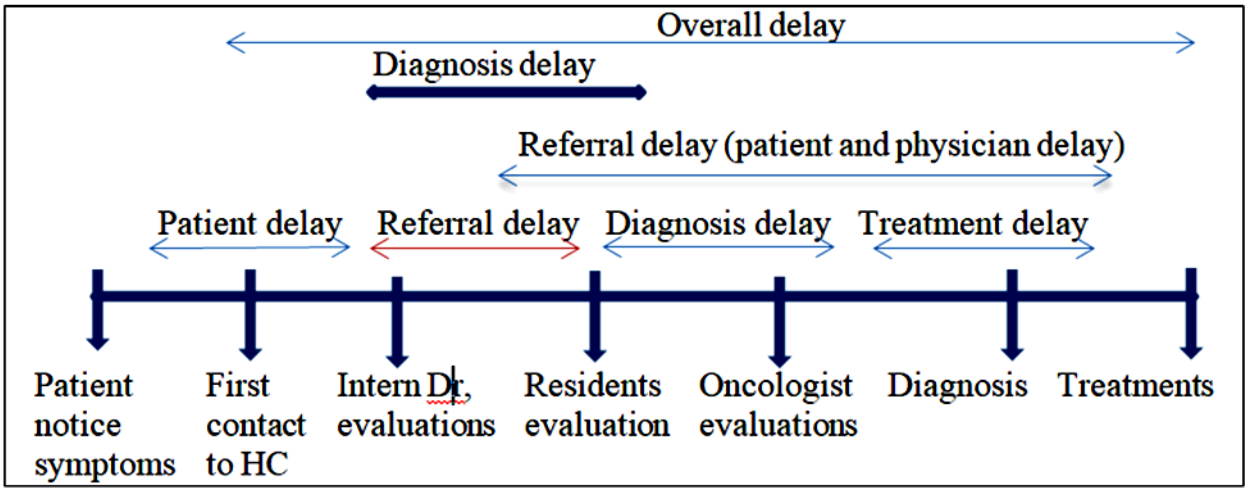
Treatment delay (TD): The time from diagnosis to the initiation of treatment (24).

Referral delay: The time between a patient's initial visit to any healthcare facility and their appointment at the UoGCSH oncology center.

Total delay (TD): The time from the first symptom to the initiation of treatment (24).

Holy water: Blessed by a religious figure.

Induction mortality: In ALL patients, induction mortality refers to the death of a patient during the initial phase of treatment, before the start of the first chemotherapy cycle (25).



HC= Health center

Figure 1: An illustration of the various types of delays that occur when seeking and receiving cancer treatment.

Eligibility criteria

All pediatric ALL patients (under the age of 18) with a confirmed pathological diagnosis who were admitted to UoGCSH were included in the study. Children who were clinically suspected of having ALL but did not receive a pathological diagnosis, or who had incomplete clinical information during their stay, were excluded.

Standard-risk (SR) ALL patients did not receive doxorubicin treatment. Due to the lack of facilities for flow cytometry (immunophenotyping) and cytogenetics (risk assessments), we categorized ALL patients as standard or high risk (HR) according to the 1993 NCI risk categorization(26).

Standard-risk ALL patients receive phases of therapy, including induction, consolidation, and maintenance. In contrast, HR patients receive additional phases, such as reinduction or intensification, before entering the maintenance phase. The four-drug combination used to treat the remaining HR patients, including CNS-positive patients, consists of prednisolone, vincristine, L-asparaginase, doxorubicin, and intrathecal methotrexate. For CNS positivity, hydrocortisone and intrathecal cytarabine are administered.

Patients between the ages of one and ten years who had a WBC count of less than 50,000/μL, exhibited no blast cell infiltration of the CNS during presentation, and showed signs of remission confirmed through bone marrow examination were considered SR ALL patients. High-risk patients were defined as those who were less than one year old or older than ten years, had a WBC count greater than 50,000/μL, or had CNS involvement or induction failure. Patients who were confirmed to have ALL based on clinical features, blood counts, peripheral blood films, and most importantly, bone marrow examination by pathologists were included.

Data collection tool and process

Data were collected using a structured questionnaire adapted from similar studies and the EFDA guidelines (16, 27-29). The questionnaire, along with a written consent form, was distributed to data collectors before the beginning of study. Measurements and responses were cross-checked for missing values, inconsistencies, and corrective measures were taken as needed. To assess delay levels, patients were asked about the time from symptom onset to first contacting a medical professional and details on delays between this contact, referral, and diagnosis. Reasons for these delays were also explored. Overall delay was calculated by summing patient and physician delays.

Data quality assurance mechanisms

To ensure data quality, the tool was initially created in English and then translated into Amharic by bilingual experts. Data collectors and supervisors received two days of training, and a pretest was conducted with 10% of the sample in non-selected hospitals, leading to tool modifications. Data collection was

closely monitored by investigators and supervisors, and data validity was assessed using statistical parameters. Adjustments were made based on pretest results.

Data analysis

Data were cleaned and coded before being entered and analyzed using Statistical Package for Social Sciences (SPSS) version 25. Descriptive statistics were used to describe frequencies, percentages, cross-tabulations, means, and medians with interquartile ranges. The strength of associations was measured using adjusted odds ratios and 95% confidence intervals. Binary logistic regression analyzed associations between independent and dependent variables, while multivariate logistic regression included variables with a significance level < 0.05 in the binary logistic regression.

Results

Sociodemographic and clinical characteristics of the study participants

A total of 90 children with newly diagnosed and admitted ALL were enrolled, with 100% response rate. Approximately 63 (70%) of the study participants were males. The minimum and maximum ages of the children were 1 year and 18 years, respectively, with a mean of 8.2 (SD= ±4.13) years. Nearly two-thirds, 57(62.2%) study participants were younger than 10 years of age. Similarly, 61 (67.8%) of the participants were rural residents. Forty-one (45.6%) of the participants were not educated. More than half of the parents, 50 (55.6%), were a farmer. Additionally, half of the parents had a monthly income below 1000 ETB, and more than three-fifths of them had health insurance. As shown in Table 1, the most common presenting symptoms were fever (86.7%), fatigue (85.6%), bone pain (78.9%), and paler (64.4%) (Table 1).

The median white blood cell count, hemoglobin, hematocrit, and platelet count were 16,450/mm3 (IQR: 5000–84,000/mm3), 8.5 g/dl (IQR: 5.6–11.05 g/dl), 23.5% (IQR: 17.2–32.9%), and 95,000/mm3 (IQR: 17.6-228,600/mm3), respectively. About 74 (82.2%) of patients were diagnosed and treated for neutropenic fever during the induction period. Twenty of the 90 children (22.2%) died before starting thiopurine chemotherapeutic drugs.

Table 1: Sociodemographic characteristics of study participants and caregivers of pediatric ALL patients at the University of Gondar Comprehensive Specialized Hospital, Northwestern Ethiopia, 2024 (n=90).

Variables	Category	Frequency	Percentage
Gender	Female	27	30
	Male	63	70
Age range in years	< 1	2	2.2
	1-10	55	61.1
	>10	33	36.7
Residence	Urban	29	32.2
	Rural	61	67.8
Health insurance	Yes	69	76.7
	No	21	23.3
Educational status of caregivers	Illiterate	41	45.6
	Primary School	29	32.2
	Secondary School	14	15.6
	College	6	6.7
Occupation of the caregiver	Unemployed	4	4.4
	Merchant	21	21.3
	private employee	3	3.3
	Governmental employee	12	13.3
	Farmer	50	55.6
Monthly income of the caregiver	No regular monthly income	50	55.6
	less than 1000,	10	11.1
	1000-3000	16	17.8
	3001-5000	5	5.6
	5001-10,000	8	8.9
	Greater than 10,000	1	1.1
Risk category at diagnosis	Standard risk	52	57.8
	High risk	38	42.2

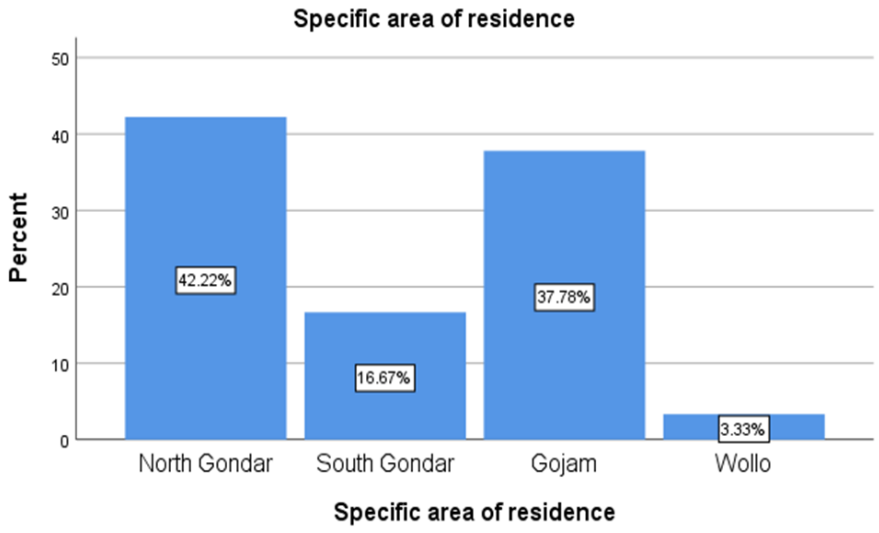


Figure 2: Specific area of residence for ALL patients at the UoGCSH Northwestern, Ethiopia, 2024 (n=90).

Table 2. Clinical characteristics of children diagnosed with ALL at presentation at the University of Gondar Comprehensive Specialized Hospital, Northwestern Ethiopia, 2024 (n=90).

Variables N= 90	Categories	Frequency	Percentage
The most common presenting symptoms	Fever	78	86.7
	Fatigue	77	85.6
	Bone pain	71	78.9
	Paler	58	64.4
	Epistaxis	35	38.9
Malaria	Yes	18	20
	No	72	80
Hemoglobin	<7 g/dl	31	34.4
	7-10 g/dl	23	25.6
	>10 g/dl	36	40
WBC counts, counts/mm^3	<4x 10^3	11	12.2
	4-49.9 x10^3	46	51.1
	≥50 x10^3	33	36.7
Platelet count	< 20k	31	34.4
	20- 150k	59	65.6
Lactate dehydrogenase level	< 1000	72	79.3
	≥ 1000	18	19.8
Frequency of BM	Once	62	68.1
	Twice	20	20.0
	≥ three times	8	8.8
ALL risk status	Standard risk	51	56.7
	High risk	39	43.3
Neutropenic fever	Yes	74	82.2
	No	16	17.8
Overall delay	< 60 day	41	45.6
	>60 day	49	54.4
Induction mortality outcome among ALL patients	Alive	70	77.8
	Died	20	22.2

Health care-related characteristics of participants

The majority of pediatric ALL patients' first contact with a healthcare provider was in health centers 43 (47.8%), followed by general hospitals 10 (11.1%), primary hospitals 21 (23.3%), private clinics 8 (8.9%), and 8 (8.9%) patients who directly visited UoGCSH. Most referrals originated from primary hospitals 29 (32.2%), specialized hospitals 23 (25.6%), or general hospitals 18 (20.0%), with some referrals coming from health centers 9 (10.0%).

Table 3. Health institutions at first visit and source of referral for pediatric ALL patients attending at the University of Gondar Comprehensive Specialized Hospital, Northwestern Ethiopia, 2024 (n=90).

Variables	Categories	Number of days delayed for referral	
		≥ 45 days	< 45 days
First facility visited	Health center	41 (95.1%)	2 (20%)
	Primary hospital	19 (23.7%)	2 (20%)
	General hospital	7 (7.7%)	3 (30%)
	Private clinic	6 (6.6%)	2 (20%)
	UoGCSH	7 (8.7%)	1 (10%)
Source for referral	Health center	8 (10%)	1 (10%)
	Primary Hospital	26 (32.5%)	3 (30)
	Specialized hospital	22 (27.5)	1(10%)
	General hospital	16 (20%)	2 (20%)
	Private clinic	8 (10%)	3 (3.3%)

Healthcare providers' specialty and initial contact evaluation at the oncology cancer treatment center

Before attending UoGCSH, 20 (21%) of the patients with ALL had already been clinically assessed for a hematological abnormality. Most patients, 68 (75.6%), were initially evaluated by interns; 11 (12.2%) were evaluated by residents; 6 (6.7%) were evaluated by general practitioners; and 5 (5.6%) were evaluated by a pediatrician. At UoGCSH, the diagnosis was made through clinical evaluation and various investigative modalities, including BM aspiration, BM biopsy, FNAC, excisional biopsy, and diagnostic imaging, depending on the clinically suspected malignancy.

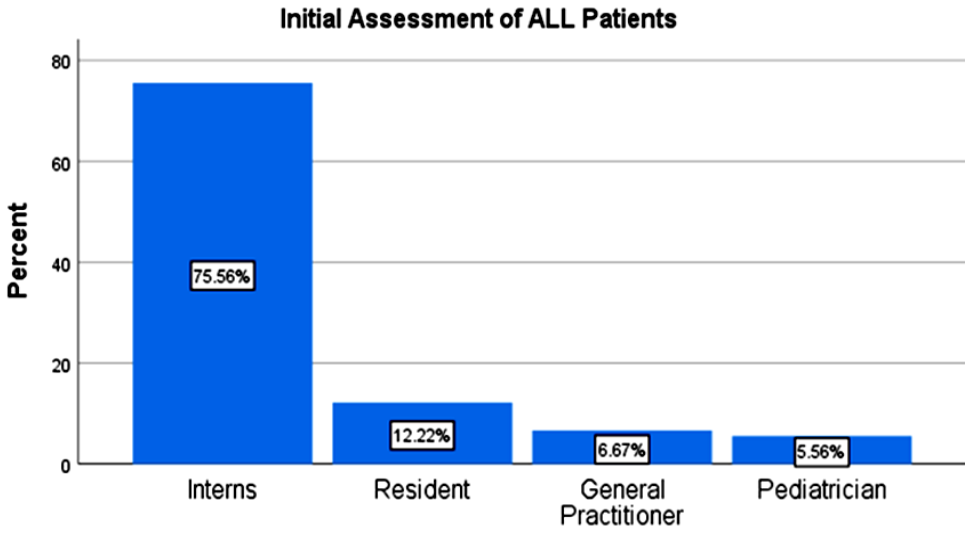


Figure 3: Patients evaluated by different healthcare providers at the University of Gondar Comprehensive Specialized Hospital in Northwestern Ethiopia, 2024 (n = 90).

Furthermore, frequent bone marrow aspirations were done for the patients. The frequency of bone marrow aspiration is one time for 62 (68.9%), two times for 20 (22.2%), and three times for 8 (8.9%) patients

Delays in diagnosis and induction chemotherapy initiation

The median time intervals for delay at the different stages of care were assessed. The overall delay from symptom onset to treatment initiation was 69 days (IQR: 47.25–85.33 days). Patient delay, from symptom onset to the first medical consultation, was 9.7 days (IQR: 7.31 –13.17 days). The median time interval for referral delay, from the first healthcare contact to arrival at the University of Gondar Comprehensive Specialized Hospital (UoGCSH), was 51.6 days (IQR: 29.00–64.33 days). The diagnosis delay, from arrival at UoGCSH to confirmed diagnosis, was 3.2 days (IQR: 2.41–4.33 days). The treatment delay, from confirmed diagnosis to treatment initiation, was 4.6 days (IQR: 3.69–6.67 days). Only 11.1% (n = 10) of patients started treatment within 30 days of the symptom onset **(Figure 4)**.

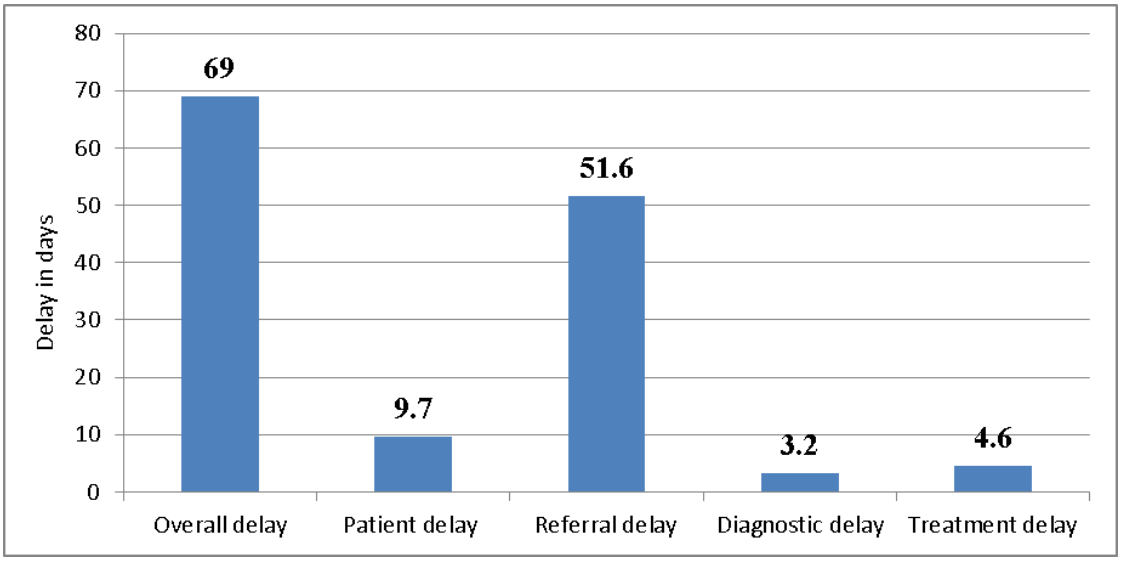


Figure 4: The median time delays in the diagnoses of childhood ALL patients at the University of Gondar Comprehensive Specialized Hospital, Northwestern Ethiopia, 2024 (n=90).

Of the 90 patients, 15 (16.7%) experienced a significant overall delay, defined as greater than 60 days (2 months). The main reasons for delayed presentation included the use of alternative medicine in 47 (52.2%) patients, limited resources in 71 (78.9%) patients, and false beliefs about cancer in 68 (75.6%) patients. The alternative treatments sought by parents included holy water in 60 (66.7%) patients, visits to herbalists in 37 (41.1%) patients, among others.

Predictors of induction mortality

Regarding the magnitude of induction mortality, 20(22.2%) children died before starting thiopurine chemotherapeutic drugs. As indicated

in the (Table 6), following univariate logistic regression analysis and screening for binary logistic regression, only 11 variables were included in the final model-one continuous variable (age in years at diagnosis) and ten categorical variables. According to the final binary logistic regression model, only malaria infection, high initial WBC, repeated BM aspiration, ALL risk status and overall delay were significantly associated with induction mortality.

Table 5. Predictors of induction mortality among pediatric children treated for ALL at the University of Gondar Compressive Speculated Hospital, Northwest Ethiopia, 2024 (n=90)

Variables	Categories	Induction treatments outcome (n=90)		COR (95%)	AOR(95%CI)
		Alive (n=70)	Died n=20)		
Age in years	<10	45(64.2%)	12(60%)	2.00	2.00
	≥ 10	25(35.7%)	8(40%)	1.200 (1.43-3.33)	1.08 (0.25-4.59)
Sex	Female	22(31.4%)	5(25%)	2.00	2.00
	Male	48 (68.5%)	15 (75%)	1.375 (1.44-4.26)	1.09(0.23-5.26)
Residence	North Gondar	30 (42.8%)	8 (40%)	1.00	1.00
	South Gondar	14 (20%)	4 (20%)	0.87(0.29-2.64)	3.78 (0.50-28.34)
	Gojam	26 (37.1%)	8 (40%)	0.93 (0.24-3.64)	3.20 (0.50-20.53)
WBC count	< 4000	10 (14.2%)	1 (1.4%)	1.00	1.00
	4000-50,000	36 (51.4%)	10 (50%)	3.75(0.42-33.63)	3.31 (0.34-9.03)
	>50,000	24 (34.2%)	9 (45%)	1.35(1.478-3.81)	5.12 (0.53-9.05)
Platelet count	< 20k	25 (35.7%)	6 (30%)	1.00	1.00
	≥20- 150k	45 (64.2%)	14/1()	1.30 (0.44-3.80)	1.85 (0.48-7.05)
Hemoglobin	<7 g/dl	23 (25.5%)	7 (70%)	2.00	2.00
	7-10 g/dl	2 (2.8%)	5 (25%)	0.96 (0.32-2.89)	0.42 (1.07-1.68)
	>10 g/dl	27(38.5%)	8 (40%)	2.22 (0.53-9.28)	0.71 (0.19-2.59)
Frequency of BM aspira-	once	49 (70%)	13 (65%)	1.00	1.00
	twice	16(22.8%)	4 (20%)	0.94 (0.27-3.31)	1.04 (1.20-5.55)
	≥Three times	5(7.1%)	3 (15%)	2.26 (1.49-10.73)	3.46 (1.50-32.71)
ALL risk status	Standard risk	43 (61.4%)	8 (40%)	1.00	1.00
	High risk	27 (38.5%)	12 (60%)	2.389 (1.765-6.597)	2.43 (1.58-8.83)
Malaria	Positive	6 (8.5%)	13 (65%)	2.00	2.00
	Negative	64 (91.4%)	7 (35%)	6.94 (3.22-14.94)	10.37 (1.64-21.50)
Use of herbalist	Yes	28 (40%)	9 (45%)	2.00	2.00
	No	42 (60%)	11 (55%)	1.227 (0.450-3.344)	1.62 (0.36-7.35)
Overall delay	<60 days	33(47%)	8 (40%)	1.00	1.00
	≥60 days	37 (53%)	12 (60%)	1.338 (1.387-3.674)	2.91 (1.94-6.37)

After controlling for all possible confounding variables, patients with malaria positivity, a white blood cell count greater than 50,000, and high-risk acute lymphoblastic leukemia (ALL) were significantly more likely to experience induction mortality compared to patients without these factors. Specifically, they were nearly ten times (adjusted odds ratio [AOR]: 10.37; 95% confidence interval [CI]: 0.064–2.150, p = 0.042), five times (AOR: 5.12; 95% CI: 0.532–9.05, p = 0.053), and 2.43 times (AOR: 2.43; 95% CI: 0.669–8.830, p = 0.038) more likely to die, respectively. Patients with an overall delay greater than 60 days were nearly 3.13 times (AOR: 3.13; 95% CI: 1.942–6.368; p = 0.042) more likely to die compared to those with a delay of 60 days or less. Additionally, patients coming from long-distance areas and those undergoing more than three bone marrow aspirations were 3.20 times (AOR: 3.203; 95% CI: 0.500–20.527; p = 0.03) and 3.58 times (AOR: 3.458; 95% CI: 0.366–32.713) more likely to die, respectively, compared to those from short-distance areas and those undergoing three or fewer BM aspirations.

Discussion

Treatment delays in leukemia can significantly impact patient outcomes, leading to increased disease progression, higher risks of complications, reduced treatment efficacy, and poorer overall survival. Factors contributing to these delays include challenges in recognizing symptoms, limited access to healthcare facilities, and inadequate diagnostic capabilities. Once a diagnosis is made, timely referral to specialized cancer centers is essential. Delays in referral may arise from a lack of awareness, transportation issues, financial constraints, or obstacles in initiating treatment. The nonspecific symptoms of acute lymphoblastic leukemia (ALL) often contribute to delayed diagnosis. Even short delays in treatment can significantly increase the risk of death and relapse. In sub-Saharan Africa, delayed presentation is common, often due to factors related to patients and referrals (20, 30).

Acute lymphoblastic leukemia is generally diagnosed more rapidly than other pediatric cancers (18). Studies demonstrate the importance of strict adherence to the protocol, as even a single day of delay significantly increases the risk of death and relapse (4). However, our study shows that more than half of the study participants experienced delays of greater than 60 days. Our study included 90 patients, 63 (70%) of whom were male. This finding is consistent with numerous previous studies (31-33). The underlying reasons for sex differences in childhood ALL risk remain unclear (34, 35). While the exact reasons for sex differences in childhood ALL are not fully understood, genetic, immune-related, and birth -related factors may play a role (35).

Treatment of childhood ALL is a major success story in hematology-oncology, with long-term survival and cure rates exceeding 90% in Western countries. However, survival outcomes in developing countries with limited resources are significantly lower. This

disparity arises from various factors, including a lack of adequate treatment centers with expertise, socioeconomic constraints, reliance on alternative medicine, variability in treatment intensity, and poor treatment adherence (16).

Other studies have shown that delays in presentation have the most significant impact on outcomes in the high-risk group, particularly before the 8th day (4). Similarly, in our study, the main reasons for delayed presentation included the use of alternative medicine in 47 (52.2%) patients, limited access to healthcare resources in 71 (78.9%) patients, and misconceptions about cancer in 68 (75.6%) patients. Alternative treatments sought by parents included holy water in 60 (66.7%) patients and visits to herbalists in 37 (41.1%) patients, among others. Moreover, the high-risk group exhibited nearly a 2.43-fold increased risk of mortality.

The magnitude of induction mortality was 22% (20/90). Twenty children died before starting thiopurine chemotherapeutic drugs. In contrast delay in induction was seen in India 52% (16). The risk of mortality and overall delay was mostly caused by the unavailability of quality pediatric cancer services, late presentation due to socioeconomic status, high treatment abandonment rates, lack of nearby pediatric oncologic centers, long travel distances to treatment centers, long wait times for care due to various delay types, the caregiver's belief that cancer cannot be cured, and lack of awareness about childhood cancer. This is in line with numerous studies (36, 37).

The median overall delay from symptom onset to treatment initiation in our study was 69 days. Compared to studies conducted in Addis Ababa (18) and Bangladesh (38), where the median overall delay was between 30 and 35 days, our results indicated a longer delay. However, our findings were comparable to studies conducted in Nigeria (39) and Kenya (40). The median referral delay to pediatric ALL oncology treatment centers in our study was 51.3 days. However, the referral delay in Tanzania was longer at 89 days (20). This extended delay may be influenced by our hospital's large catchment area and high patient volume, which result in longer wait times for care. Additionally, residing outside urban areas was significantly associated with increased overall delays.

In our study, we further categorized delays within the healthcare system as diagnostic and treatment delays. Another aspect of healthcare system delay is the delay in initiating treatment after a diagnosis is established. Our median diagnostic and treatment delays were 3.2 and 4.6 days, respectively. . Compared to a study conducted in Addis Ababa (18), where the median diagnosis and treatment delay of 11 and 8.5 days, respectively, our delay were notably shorter. Although our overall delay is not directly comparable, the median delay in diagnosis and treatment in our study was shorter than that reported in studies conducted in Egypt, (41) Canada, (42) and India (16). Despite the longer overall delays, treatment initiation was not significantly delayed in our

setting due to prompt ward admission. Comparing our results with other studies is challenging because they define "diagnosis delay" as the time from initial healthcare contact to cancer diagnosis.

Our study found that 67.8% of patients from rural areas delayed seeking medical care for over a month. Contributing factors might be include reliance on alternative medicine, long wait times, low confidence in healthcare quality, inadequate provider knowledge about ALL treatments, and limited access to diagnostic services. Similar delays have been reported, in Tanzania (20), Ghana (43), and Ethiopia (4, 14, 44) often linked to consulting traditional healers or late diagnosis.

Our report showed a 22% induction mortality rate, higher than the 5% seen in recent clinical trials (45) but lower than the 30% in Kenya (4). We didn't explore specific causes of death, but high-risk patients had nearly three times the mortality rate of standard-risk patients (45-47). Common treatment-related deaths include sepsis, central nervous system issues, infections, and complications from delays or treatment toxicity (46). Key factors linked to mortality include weight-for-age, immunophenotype, reason for admission, and neutrophil count (48, 49). Our study also assessed how overall treatment delays nearly three times affect mortality rate.

Despite extensive research on children with acute lymphoblastic leukemia, there is limited analysis on how chemotherapy delays impact survival. The relationship between overall treatment delays and induction mortality is significant but not fully understood. To improve outcomes, it's crucial to enhance timely presentation and early treatment initiation. This can be achieved by educating healthcare providers about leukemia symptoms, improving bone marrow sampling and diagnostic processes, and addressing patients' economic needs. In northern Ethiopia, delays in the referral process exacerbate these issues for pediatric cancer patients.

Conclusion

Strict adherence to specific timing in ALL treatment protocols is crucial for patient survival. Our study highlighted significant referral delays in diagnosing childhood ALL, influenced by factors such as residency, socioeconomic status, parental education, alternative medicine use, and healthcare provider perceptions. To address these issues, it's important to increase awareness among the public, parents, and healthcare providers about childhood cancer. Improving the referral process and enhancing education for both healthcare providers and community members can help reduce these delays and lower the ALL mortality rate.

Declaration

Ethical considerations

The study protocol was approved by the ethical review board of the University of Gondar (Rfe. VP/RTT/05/246/2022). Study participants were informed that participation was voluntary and that all gathered information would be handled confidentially and analyzed collectively. Privacy and confidentiality of

collected information were ensured at all levels through de-identification, password-protected computers, and the storage of questionnaires in a lockable cabinet. Informed consent was obtained in accordance with the current revision of the Declaration of Helsinki.

Acknowledgments

We express our gratitude to the University of Gondar Comprehensive Specialized Hospital. We also thank the data collectors for their participation in the data collection and cleaning process.

Data availability

All data generated or analyzed during this study are included in the manuscript. Additionally, the datasets used and/or analyzed (SPSS data) are available from the corresponding author upon reasonable request.

Abbreviations

ALL: acute lymphoblastic leukemia

TPMT: Thiopurinemythyltransferase

ADR: adverse drug reaction

EFDA: Ethiopian Food and Drug Administration

HCPs: Health care professionals

UoGCSH: University of Gondar Comprehensive Specialized Hospital

MOH: Ministry of Health

SPSS: Statistical Package for Social Sciences

STG: Standard Treatment Guidelines

WHO: World Health Organization.

Consent

Written informed consent was obtained from all the participants.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Funding

None

Authors' Contributions

E.K. data curation, validation, writing–review & editing, data analysis, prepared tables and figures. M.A. conceptualization, data curation, methodology, review & editing. M.B. formal analysis, project administration, resources. A.G. formal analysis, writing–original draft, writing–review & editing. A.M.G. conceptualization, data curation. D.T. investigation, validation. H.A. conceptualization and data curation. A.M. methodology. E.T. investigation, resources. N.B. conceptualization, project administration, methodology, supervision, validation, writing -review & editing. All authors read and approved the final manuscript.

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