JIMMA UNIVERSITY INSTITUTE OF HEALTH SCIENCE SCHOOL OF MEDICINE DEPARTMENT OF PEDIATRICS AND CHILD HEALTH

Time to outcome of acute lymphoblastic leukemia and its associated factors among pediatrics diagnosed at Jimma university medical center pediatric Oncology unit (JUMC-POU), south west Ethiopia, August 2016 to August 2022

BY: Gada Hirko (MD, Pediatrics Resident)

A Research to be submitted to the Department of Pediatrics and Child Health, Jimma University Medical Center as a partial fulfillment for specialty certificate in Pediatrics and Child Health.

JIMMA UNIVERSITY INSTITUTE OF HEALTH SCIENCE SCHOOL OF MEDICINE DEPARTMENT OF PEDIATRICS AND CHILD HEALTH

Time to outcome of acute lymphoblastic leukemia and its associated factors among pediatrics diagnosed at Jimma University medical center pediatric Oncology unit (JUMC-POU), South west Ethiopia, August 2016 to august 2022

Investigator:

Gada Hirko (MD, Pediatrics' Resident)

Advisors:

1) **Dr. Diriba Fufa (MD, MSc, Pediatric Oncologist and Hematologist)**
2) **Zerihun Kura (MSc, Epidemiology-Biostatistics)**

March, 2022

JIMMA, OROMIA, ETHIOPIA

DECLARATION

ASSURANCE OF PRINCIPAL INVESTIGATOR

The undersigned agrees to accept responsibility for the scientific ethical and technical conduct of the research project and for provision of required progress reports as per terms and conditions of the faculty of Medical Sciences in effect at the time of grant is forwarded as the result of this application.

Name of the investigator: **Gada Hirko**

Date: _____ Signature: _____

APPROVAL OF THE ADVISORS

Name of the advisor: **Dr. Diriba Fufa**

Date: _____ Signature: _____

Name of the advisor: **Zarihun Kura**

Date: _____ Signature: _____

SUMMARY

Background: Despite the significant improving of treatment outcomes and survival rates of pediatric diagnosed with acute lymphoblastic Leukemia (ALL) in developed country, it remained very low in developing countries.

This study aims to determine the Time to Outcome of pediatrics diagnosed with ALL at Jimma university medical center pediatric Oncology unit (JUMC-POU) in its first six years of the unit`s establishment.

Objective: The objective of the study was to assess the Time of Outcome of pediatrics diagnosed with ALL and associated factors at JUMC-POU, South West Ethiopia

Methods: A retrospective study design was conducted. The lists of the patients were obtained from the data base in the unit to retrieve the patient chart. Data was collected using a semi-structured questionnaire. The data entered into Epidata manager version 3.1, and then exported to SPSS version 26 for analysis. Statistical significance was considered at a p-value of less than 0.05.

Event-free survival were estimated by Kaplan–Meier analysis and compared using the log-rank test. A Cox proportional hazards model was used to identify independent prognostic factors; and finally multivariate Cox regression model used to report the significance and association.

Results: A total of 117 pediatrics diagnosed with ALL from August 2016 to august 2022; from these 108 patients, whom their charts retrieved, were enrolled in the study. There were 36.1% treatment abandon, 37.9% death and 7.4% completed treatment.

Around 66% patients completed induction and achieve remission, and the three years event free survival in our study was 39%.

Recommendation: Prospective collection of patient data to overcome missing information.

Strengthen the supportive care to avert preventable treatment and diseases related morbidities such as infection, hemorrhage, and TLS.

Strengthen psychosocial support to avert treatment abandonment

Keywords: Complete Remission, Relapse, and Refractory (resistant) disease, pediatrics ALL, time to outcome:

ACKNOWLEDGEMENT

First, I would like to thank Jimma University Post graduate studies coordinating office and department of Pediatrics and Child health, Faculty of Medical Sciences, Jimma University for giving me this golden opportunity to do this research.

I would like to express my deepest gratitude and appreciation to my advisors Dr. Diriba Fufaa (MD, Pediatric Oncologist and Hematologist) and Mr Zerihun Kura (Ms. Epidemiology-Biostatistics) for their unreserved encouragement and provision of constructive comments and guidance while developing this research proposal to the final result.

CONTENTS

LIST OF TABLES

LIST OF FIGURES and Graphs

LIST OF ABBREVIATIONS AND ACRONYMS

ALL	Acute Lymphoblastic Leukaemia
BM	Bone Marrow
BMI	Body mass index
DSF	Disease-free survival
EFS	Event-free survival
RFT	Renal Function Test
CSF	Cerebra-spinal fluid
DC	Data collector
ETB	Ethiopian Birr
FAB	French-American-British
GP	General Practitioner
HMIS	Health Management Information System
JU	Jimma University
JUERC	Jimma university Ethical Review Committee
JMC	Jimma Medical Centre
HICs	High income countries
LMICs	Low and middle-income Countries
PI	Principal investigator
MRD	Minimal residual diseases
MUAC	Mid upper arm circumference
OAS	Overall survival
OFT	Organ function test
SPSS	Software Program for Social Science
SSA	Sub-Saharan Africa
SMS	Superior mediastinal syndrome
SVCS	Superior venacaval syndrome
TLS	Tumour Lysis Syndrome
USA	United States of America
WHO	World Health Organization
WFH	Weight for height

1.1. Background

Acute lymphoblastic leukemia (ALL) is the most common malignancy in children. It accounts one fourth of all childhood cancers and approximately 75% of all case of childhood leukemia[1]. ALL is diagnosed when bone marrow (BM) contains at least 25% lymphoblast's excluding those with mature B-cell phenotype. Diagnosis of ALL is based on standard French American-British (FAB) morphologic and cytochemical criteria[2]–[5].

In the globe, the incidence of ALL cases increased from $49.07*10^3$ in 1990 to $64.19*10^3$ in 2017. However, the age-standardized incidence rate, ASIR (per 100,000 individuals) kept stable (from 0.89 in 1990 to 0.85 in 2017). The incidence of ALL cases at Eastern Sub-Saharan Africa-1.86 (1.06~3.43) $*10^3$ in 1970 and 3.69 (2.76~5.15) * 10^3 cases in 2017[6].

Recently in 2015, a population-based cancer estimation done in Ethiopia stated that around 957 ALL cases in children diagnosed each year [7].

Contemporary treatment of childhood acute lymphoblastic leukemia (ALL) results in long-term survival in over 90% of children today [7]. However, less than 60% of children worldwide even have access to cancer treatment and outcomes for ALL in low-income countries remain poor [8].

The reason increased survival in HICs and decreased mortality from ALL is due to increased awareness of the general population about cancer, availability of advanced diagnostic and treatment means, as well as existence of well-trained professionals in the field[8].

There are also advances in clinical and biologic characterization, development of risk-adapted therapies, and the optimization of supportive care have resulted in a dramatic increase in the cure rates of children with cancer over the last four decades[9], [10].

Even though ALL treatment outcome and survival rate are improving significantly in western, in developing countries, survival rate for pediatrics with ALL is still low because of poor infection control, delay in consultation, late presentation, high dropout rate, treatment-related complications, and low socioeconomic status is some identified problems[11]–[17].

To improve outcome of children living in LMICs regional collaborative initiatives have been developed in Central and South America and the Caribbean, Africa, the Middle East, Asia, and Oceania. These initiatives integrate regional capacity building, education of health care providers, implementation of intensity-graduated treatments and establishment of research programs that are adjusted to local capacity and local needs[18].

Twinning Programs and Mentoring Relationships, a collaborative relationship between a university department or cancer program in HICs and a cancer program/facility in a LMICs, established by International Cancer Expert Corps in order to make network-oriented global partnership that emphasizes sustainability and growth. This capacity building strategy facilitates the creation of a sustainable platform for the sharing of best practices and learnings from each other through information and technology transfer[19].

In order to close these survival gap, WHO also launched Global Initiative for Childhood Cancer in September 2018 with its first focus of the six common cancers including ALL, highly curable with proven therapies that together represent 50–60% of all childhood cancers. The goal of the initiative is to achieve at least a 60% survival and to reduce suffering for all children with cancer by 2030[20].

Specifically in Ethiopia, prior to 2013 there was no dedicated pediatric hematology-oncology (PHO) programs existed. In order to improve this Aslan Project, a US nonprofit organization initiative, was established pediatric cancer care in Ethiopia. First, in 2013 at Tikur Anbessa Specialized Hospital (TASH) in collaboration with the FMOH and Addis Ababa University (AAU), and second at Jimma, JUMC in southwestern Ethiopia in 2016, pediatric oncology unit and PHO fellowship program established. PHO services in Ethiopia are now in operation with varying levels of capacity at five government hospitals, but an estimated 80% of children with cancer in Ethiopia are still not being diagnosed or referred to a PHO treatment center[21].

1.2 Statement of the Problem

Significant progress has been made in diagnosis and treatment of childhood cancers especially in resource-rich countries, but most resource-poor countries still lag behind[22] In Sub-Saharan Africa, data on childhood ALL are extremely rare because of a shortage of trained personnel and inadequate diagnostic facilities. Its prognosis also remains poor in most African countries with a survival rate rarely reaching 15%. This poor outcome is most often due to a delay in care, availability of cancer drugs, poor infection control practice and a high drop-out rate[14], [16], [17]

The purpose of this study is to determine Time to outcome and associated factors of ALL among children and adolescent admitted by identifying socio-demographic factors, delay before hospital visited, clinical and laboratory profile at presentation and type of chemotherapeutic regimen given which considered very relent for decision making on how to improve the outcome of ALL.

1.3 Significance of study

The outcome of ALL in children can be affected by socioeconomic status of parents/ caregivers, knowledge & attitude of parents/caregivers, health system and chemotherapy related factors. Even though ALL is the commonest child hood malignancy, and having huge burden on family and patients, there are few studies done regarding outcome and its associated factors in developing country in general & so far there are no studies done in our country/ setting on this line.

Taking it in to account the existing problem under study, which is a critical, and major public health problem and having limited information because of lack of published study on the outcome and associated factors of patients with ALL in the study area in particular and very few studies in developing countries farther strengthen the need of this study.

Studies conducted elsewhere in other countries could not be used to infer about outcome and associated factors among children and adolescent with ALL in Ethiopia or JUMCPOU. Therefore, to address this problem, it is believed that this work will provide up-to-date information with regards to outcome and associated factors of ALL among the study population. So, this study will provide a baseline data for future studies and can serve as the comparison reference for childhood cancer program development at JUMC-POU and will also call attention of health workers and planners to give due attention to improving the management depend on study result.

2. 1. LITERATURE REVIEW

According to study done at Hematology/Oncology Unit, Department of Pediatrics, University of Athens, of the 47 children with diagnoses between 1994 and 1996, all patients achieved complete remission. Twenty-nine patients(62%) were classified as having high-risk disease, two of whom showed central nervous system disease at diagnosis. One boy died of a systematic infection during induction and two children died during the consolidation phase. Eighteen children (38%) had good-risk ALL. No consolidation deaths occurred. Two patients died in in the maintenance phase, two died of infections[23].

Study done by Nordic Society of Paediatric Haematology and Oncology-ALL92 protocol included 1652 patients < or =15 years of age with precursor B- and T-cell ALL diagnosed between 1992 and 2001. Induction deaths and deaths in first complete remission (CR1) were included in the study. A total of 56 deaths (3%) were identified: 19 died during induction (1%) and 37 in CR1 (2%). Infection was the major cause of death in 38 cases. Five patients died of early death before initiation of cytotoxic therapy. Five patients died because of toxicity of inner organs and one of accidental procedure failures. Seven patients died of complications following allogenic haematopoietic stem cell transplantation (HSCT) in CR1[24].

In Poland ALL was diagnosed in 100 children (44 girls, 56 boys; 1-18 years of age) in the Department of Pediatric Hematology and Oncology, Warsaw Medical University, over the period from November 2002 to November 2006. According to the ALL-IC 2002 protocol the patients were divided into three risk groups: SR-standard, IR-intermediate and HR-high. out of the 100 patients qualified for treatment regimens according to the ALL-IC 2002 protocol, 97 entered remission, 11 died and 3 had a relapse. Under the ALL-IC 2002 protocol these children were stratified into the following groups: SR-31%, IR-44% and HR-25%[25].

A retrospective analysis of data of children with ALL at two centers, of the university hospitals of Uludağ University (Bursa) and Dokuz Eylül University (İzmir), from Turkey, diagnosed and treated between January 1995 and January 2010 according to the original ALL-BFM95 protocol in the pediatric hematology clinics. A total of 343 children, aged between 1 and 18 years old, 200 male,and 143 female: good predinisolone response 298(87%), CR was

achieved in 333 of 343 patients (97 %); while 5 patients (1.5 %) had M2/M3 marrow at the end of the induction treatment. Five patients (1.5 %) died during induction treatment due to infection or disease complications; relapse rate was found to be 14.8 %; death rate was found to be 20.1 % in this study[11].

A retrospective study done among the medical records of children hospitalized for ALL between November 2009 and October 2011 in the pilot Paediatric Oncology Unit at the Charles de Gaulle University Pediatric Hospital Center, in Ouagadougou (Burkina Faso) a total, nine children with ALL were hospitalized during the two year study period. The average age of patients was 10.77± 2.82 years. They were predominantly male. The average time of hospitalization was 43.11 days ± 39.54 days. Eight patients underwent chemotherapy according the protocol of FAPOG 2005. Children's evolution was favorable in two patients who experienced remission, four patients had treatment failure. Six patients died[12].

A retrospective medical records and cross-sectional study done at Kenyan academic hospital the treatment outcomes of 136 children diagnosed with ALL between 2010 and 2016. The treatment outcomes were death (30%), progressive or relapsed disease (26%) and abandonment (24%). Of all deaths, 80% were early deaths (prior or during induction), whereas 20% occurred in remission[13].

In Malawi twenty patients (11 boys, 9 girls) with a median age of 7.3 years were treated between December 2009 and August 2011. Two children, both with a high WBC, died before treatment could be administered. A further 7 patients died during induction therapy. Among the 11 patients that completed induction therapy, all achieved a morphological remission by Day 28. Maintenance therapy was well tolerated and 2 children completed therapy. Five children had presumed relapses during maintenance (3 confirmed by bone marrow examination) and 2 after completion of treatment (one confirmed on bone marrow examination), all of whom died of their disease. One patient died of presumed bacterial meningitis during maintenance[14].

A retrospective, descriptive study done from January 1, 2010 to December 31, 2014, on 33 children, age 2 to 15 years with ALL, treated at the pediatric oncology unit of Bamako, Mali, according to a protocol developped by the French African Pediatric Oncology Group

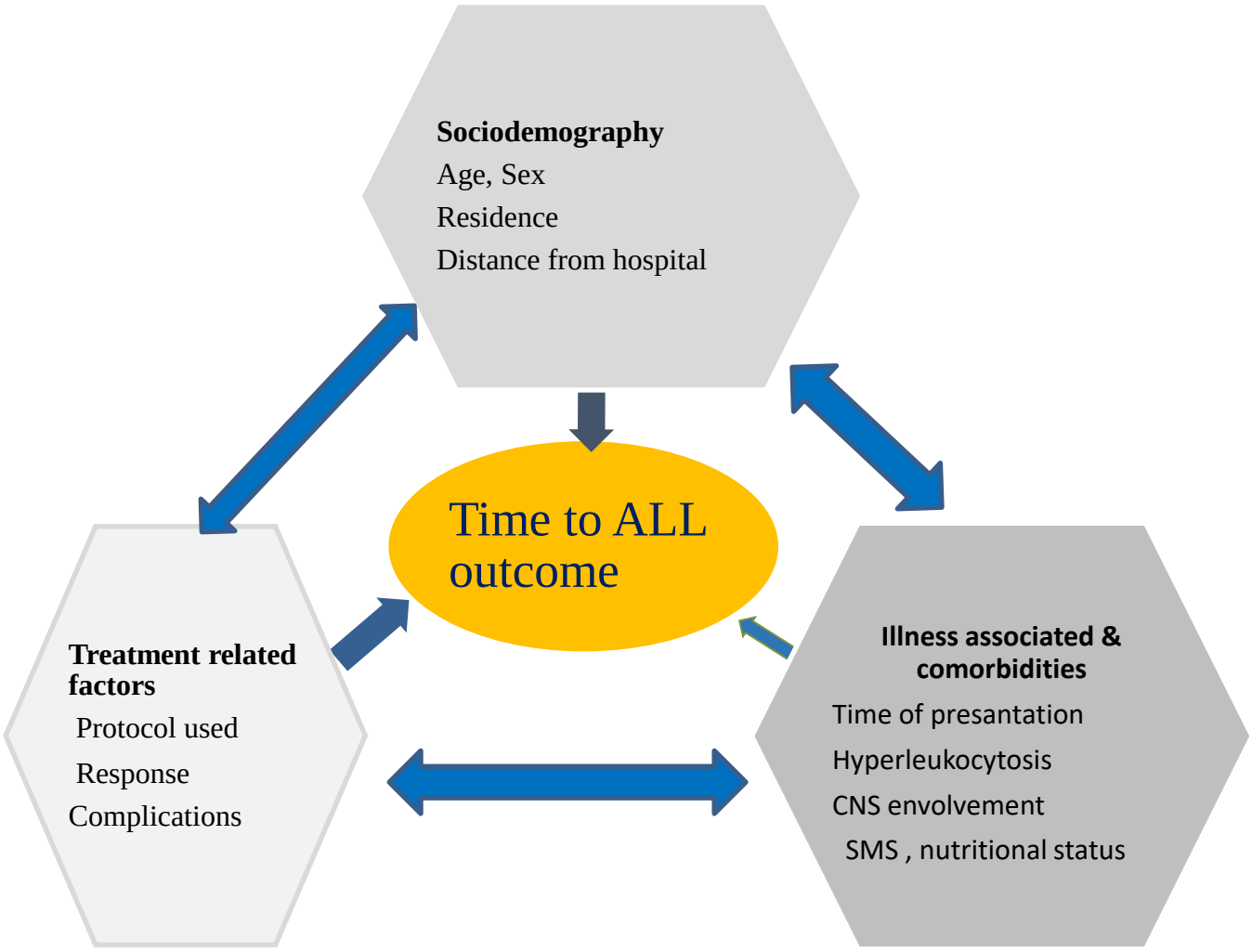
(FAPOG). Complete remission at the end of induction was 64%, with 27% of early deaths. After a mean follow-up time of two years, the study recorded 12% of loss of follow-up and 82% of deaths. The overal survival was 6. In this study, deaths were due to infectious and or drugs toxicities (57%), unlike in developed countries where deaths are generally due to relapses. This high mortality rate could also be explained by the inadequacy of the proposed protocol, the late diagnosis, the difficulties of access to supportive care and the irregularity in the monitoring of treatment[15].

Study conducted at Gondar University Hospital, Northern Ethiopia, among children aged below 15 years old admitted from September 2010 to August 2013 a total of 71 cancer cases were diagnosed. Nearly half of patients had not received chemotherapy and majority of those started chemotherapy did not complete all the treatment cycles. Shortage and absence of safe and affordable chemotherapy drugs were the major reasons for therapy interruption[17].

2.1. Conceptual frame work

In the conceptualization of this study, different factors like age, sex, WBC number at diagnosis and other factors can affect the outcome of ALL. Other factors like, response for chemotherapy after induction, and nutritional status of the patients will have an effect on the ALL prognosis.

Fig 1: Conceptual frame work (developed by principal investigator)



3. OBJECTIVES OF THE STUDY

3.1. General objective

- To Assess time to Outcome in pediatrics with acute lymphoblastic Leukemia and its associated factors at Jimma University Medical Centre Pediatric Oncology Unit (JUMC-POU), South West Ethiopia, from August 2016 to August 2022

3.2. Specific objectives

- To determine the time to Outcome of pediatrics diagnosed with acute lymphoblastic Leukemia at Jimma University Medical Center Pediatric Oncology Unit (JUMC-POU) during the study period.
- To determine associated factors of time to outcome of ALL among children and Adolescent.

4. METHODS AND PARTICIPANTS

4.1 Study area and period

This study was conducted from May 08- Sep 05, 2022 in Jimma Medical Centre (JMC), Jimma, Oromia South West Ethiopia. The center is one of the oldest public hospitals in the country located in Jimma town of Oromia Regional State, Ethiopia. Jimma town is located around 352 km far away from Addis Ababa.

JMC is used as a referral and specialized medical center; located in the out skirt of the Jimma town, it gives services for an estimated 20 million people from Jimma zone and the catchment population, particularly the south western Oromia and as referral centre for regions of South Western part of Ethiopia including Gambelia and Southern Nations Nationalities and People (SNNP) Regional states.

With a bed size of 800, JMC provides services for approximately 15,000 inpatient, 160,000 outpatient attendants, 11,000 emergency cases and 4,500 deliveries per year coming to the hospital. It also serves as teaching hospital for several undergraduate and post graduate programs in the field of basic sciences as well as clinical medicine for health science students of Jimma University. The hospital has many Inpatient service for both children and adult patients (Critical wards, ICU, Oncology, cardiac, gyn. and obs., etc.).

Pediatrics department has a total of 120 beds for which pediatric oncology has 24 isolated beds as a unit. The unit started to provide services August 2016 and seen more than 600 patients since then. The unit utilizes the resource adapted protocol adapted for INCTR –Protocol to treat acute lymphoblastic lymphoma.

4.2 Study design

A facility based retrospective study design will be employed.

4.3 Populations

4.3.1 Source population

Children and adolescent admitted to Pediatrics' Oncology ward of JMC

4.3.2 Study population

All paediatrics diagnosed to have Acute Lymphoblastic Leukaemia at JUMC Pediatrics' Oncology Unit.

4.3.3 Inclusion and exclusion criteria

Inclusion criteria

- Paediatrics diagnosed with Acute Lymphoblastic Leukemia admitted to Pediatrics Oncology Unit, JMC.
- Patients who were more than one month since diagnoses during the data collection

Exclusion criteria

- Document was lacking major information like age, sex, date of diagnoses and treatment given.

4.3.4 Sample size determination and sampling techniques

All pediatrics diagnosed with ALL from August 2016- August 2022 will be enrolled.

4.4 Study variables

Independent variable

Socio-demographic:

- Age, Sex, Distance from JUMC

Anthropometry

- MUAC, WFH, BMI, WFA, HFA

Laboratory and clinical profiles:

- Duration of illness
- WBC at presentation
- CNS status
- TLS
- Liver and spleen size

Complications:

- Bleeding, NF, NNF, Mucositis…

Outcome

- Abandon, death, relapse, on treatment, completed treatment

Dependent Variable

- Time to outcome of ALL

4.5 Data collection tools and procedures

Ward log books from Pediatric Oncology ward was used to obtain medical record numbers of the patients diagnosed and treated for acute lymphoblastic leukemia.

And those patients who were confirmed to have acute lymphoblastic leukemia based on clinical features, blood counts, peripheral blood films and most importantly bone marrow examination either by pathologist or hematologist were included.

Subsequently, specific information from the medical chart were filled on structured questionnaire prepared for this purpose.

The cases ware characterized with respect to age, sex, treatment status and outcome of treatment.

4.6 Processing & analysis

After data collected it was edited and coded for analysis. The data entered into Epidata manager version 3.1, and then exported to SPSS version 26 for analysis. Data analysis was done using the SPSS statistical software version 26. Frequency tables and graphs were used to express the results.

The probability of event-free survival was estimated by the method of Kaplan and Meier; estimates were compared using the log-rank test. Event-free survival was measured from the date when the patient start chemotherapy to the first event (death or relapsed leukemia) or the date of last follow-up.

4.7 Ethical consideration

Ethical clearance was obtained from Institutional Review Board (IRB) of Institute of Health of Jimma University; confidentiality of information collected from each study documents were maintained at all levels. All steps in data collection and compilation were conducted and supervised by the principal investigator. Strict confidentiality assured through anonymous recording and coding of questionnaires and placed in a safe place.

4.8 Dissemination and Utilization of Results

The result of the study was presented to the department of pediatrics and child health, Jimma University. The final result from the study submitted to the Research and Postgraduate Office, Jimma University in a form of written report. Subsequently, the study result published on peer reviewed journal.

4.8 Operational definitions and Variable measurements

- Complete Remission- defined as the eradication of all detectable leukemia cells (less than 5 percent blasts) from the bone marrow and blood and the restoration of normal hematopoiesis (>25 percent cellularity and normal peripheral blood counts)
- Event free survival (EFS): The time from diagnosis to the first appearance of relapse/death or August 16, 2022 (cut-off date).
- Relapse- the reappearance of leukemia cells in the bone marrow or peripheral blood after the attainment of a complete remission.
- Refractory (resistant) disease: defined as those patients who fail to obtain a CR with induction therapy i.e., failure to eradicate all detectable leukemia cells (less than 5 percent blasts) from the bone marrow and blood with subsequent restoration of normal hematopoiesis (greater than 25 percent marrow cellularity and normal peripheral blood counts).
- Treatment related death: complication such as infection, TLS or bleeding caused by treatment;
- Diseases progression related death: death due to complication of the disease but not related to treatment complications
- CNS Involvement- ≥5 cells/mm3 of CSF analysis

5. Result

Socio-demographic characteristics

A total of 117 pediatric patients diagnosed with acute lymphoblastic leukemia to the unit from August 2016 to August 2022 from which 108(92.3%) charts were able to be retrieved. 94(88.6%) of the diagnosed was made by bone marrow aspiration histology while 14(11.3%) diagnosed by peripheral blood smear histology

There was a slight male predominance with a total of 65 (55.6%) males and 52(44.4%) females. Majority of patients were in age range between 1 year & 10 years. (See table: 1.) Regarding the geographical distribution of the patients, 94(80.3%) of them were from Oromia region, 19(16.2%) from SNNPR region and 2(1.7%) came from Gambella. From these 80(68.3%) of them resides in rural. The distance from JUMC was estimated by using google map & the documented nearest city on patient folder which ranges from 0 to 441 KM with median 70 ± 111 KM.

Table 1: Socio-demographic characteristics of pediatrics diagnosed with ALL at JUMC-POU from August 2016 to 2022

Variables	Categories	Frequency(n=117)	Percent
Sex	Male	65	55.6
	Female	52	44.4
Age	0-12mo	5	4.3
	>120mo	41	35
	1-10yr	71	60.7
Religion of care giver	Christian	44	37.6
	Muslim	73	62.4
Residence of care Givers	Rural	80	68.3
	Urban	37	31.7
Region	Oromia	94	80.3
	SNN	19	16.2
	Gambella	2	1.7
	Not documented	1	1
Distance	<25KM	29	25.0
	25-50KM	35	29.8
	50-100KM	6	4.8
	>100KM	47	40.3

Clinical and Laboratory profiles of patients at presentation

The duration of illness at the time of presentation ranges from 02 days to 321 days. The median duration of illness at presentation was 30 days (SD±44 days).

The nutritional status of 50(48.1%) patients was moderate to severe acute malnutrition. At presentation 7(6.7%) patients were having CNS involvement clinically (cranial nerve palsy, paraplegia, or visual loss without leukocytosis); and 5(4.8%) patients had superior mediastinum syndrome or mediastinum widening on imaging either by Chest X -ray or CT scan. The WBC at admission was less than 50,000/micro-Littre in 69(66.3%) patients.

Table 2: Laboratory & clinical profiles at admission among pediatrics treated for ALL at JUMC-POU from August 2016 to 2022

Variables	**Description**	**Count(n=108)**	**Percentage**
WBC/mic. L.	Less than 50000	72	66.6
	Greater than 50,000	32	29.6
	Not documented	4	3.7
NEUT.	Greater than 1500	30	27.7
	1000-1500	8	7.4
	500-1000	15	13.9
	<500	51	47.1
	Not documented	4	3.7
Hgb	Normal for age	6	5.5
	Mod. Anemia	38	35.2
	Severe anemia	60	55.5
	Not documented	4	3.7
PLT	>150,000	10	9.2
	20,000-15000	45	41.6
	<20,000	49	45.3
	Not documented	4	3.7
Nutritional status	Well nourished	54	50
	Moderate acute malnutrition	18	16.7
	Severe acute malnutrition	36	33.3

Treatment outcome and related problems

Table 3: Treatment protocol used in our facility, adopted from INCTR-USA ALL protocol

A. Prophase:	B. Induction:
Prednisone 60mg/m2 /day, TID for 7 days. Intrathecal (IT) Methotrexate (Day 1)	✓ Vincristine 1.4 mg/m2 IV (on day: 8, 15, 22, 29) ✓ Prednisone 60 mg/m2/ day PO TID (from day 8-28) ✓ Asparaginase 6000 U/m2, IM x 9 doses ✓ Intrathecal Methotrexate Days 8 and 29; ❖ Doxorubicin/ Daunorubicin for HR was given for 27 patients.
C. **Consolidation Standard Risk:**	D. Consolidation High Risk:
✓ Vincristine 1.4 mg/m² IV on Day 1 ✓ 6-Mercaptopurine 75 mg/m2 PO daily days 1-28, Intrathecal Methotrexate on days 1, 8, and 15	➢ Cyclophosphamide 1000 mg/m² IV Days 1 & 29 ➢ Cytosine Arabinoside (Ara-C) 75 mg/m²/day IV Days 1-4, 8-11, 29-34, 37-41 ➢ Mercaptopurine 60 mg/m²/day PO Days 1-28, ➢ Vincristine 1.4 mg/m2 IV x 2 weekly on days 15 and 22 ➢ E Coli Asparaginase 6000u/m2 /dose IM x 6 doses starting on day 15 –every 2nd day ➢ IT Methotrexate Once a week x 4 Days 1, 8, 15, 22
E. Interim maintenance (8 weeks) therapy for Standard Risk	**E. Delayed intensification (8 weeks)**
✓ Dexamethasone 6 mg/m²/day PO on Days 1-5 and 29-33. ✓ Vincristine 1.4 mg/m² IV push Days 1 and 29. ✓ Mercaptopurine 75 mg/m²/day PO on Days 1-50; ✓ Methotrexate 20 mg/m2 PO on Days 1, 8, 15, 22, 36, 43, 50. ✓ Intrathecal Methotrexate on Day 29 for all patients.	• Dexa 10 mg/m²/day PO, Days 1-7, 15-21 BID • Vincristine 1.4 mg/m² IV push Days 1, 8, 15. • Doxorubicin 25 mg/m² IV Days 1, 8, 15. given • L'Asparaginase 6000 IU/m² IM x 6 doses Begin Day 4 and adjust administration for a Mon-Wed-Fri schedule. • Cyclophosphamide 1,000 mg/m² IV over 20-30 min, Day 29. • 6-MP 60 mg/m²/day PO Days 29-43 • Cytarabine 75 mg/m²/day IV push or SC x 8 total doses, Days 29-32 and 36-39. • Intrathecal Methotrexate on Days 1, 29 and 36
F. Maintenance regimen (84 days with 8-10 cycle)	
✓ Vincristine 1.4 mg/m² IV Days 1, 29 & 57. ✓ Dexa. 6 mg/m²/day PO, Days 1-5, 29-33, 57-61. ✓ Oral Mercaptopurine 75 mg/m²/day PO Days 1-84 ✓ Methotrexate 20 mg/m²/week PO Days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78 ✓ Intrathecal Methotrexate on Day 1. ❖ Given also on day 29 of first 4 maintenance cycles for patients with HR, in terms of PO MxT	

Some adjustments:

- For the first year 3 drug induction was used.
- Induction- IT-MxT 4 doses weekly for suspected CNS involvement
- Maintenance: 6-MP or MxT PO will adjust based on the CBC result.

Follow up:

- Peripheral blood smear- on day 8 of prophase
- BMA- day 29 for risk stratification and response

Allopurinol 400mg/m2 /day in 3 divided doses orally for 5 days starting 24 hours before first prednisone dose unless chemotherapy needs to be started urgently for hyper-leukocytosis.

From those 108 patients diagnosed with ALL during the study period 99(91.7%) of them started chemotherapy 9(8.3%) of them did not start the treatment. The family declined the treatment in three patients, four of them dead before the treatment commencement and two of them referred to Tikur Anbessa Specialized Hospital. The rest 9 patient's treatment status was not known, since their chart was lost and difficult to analysis.

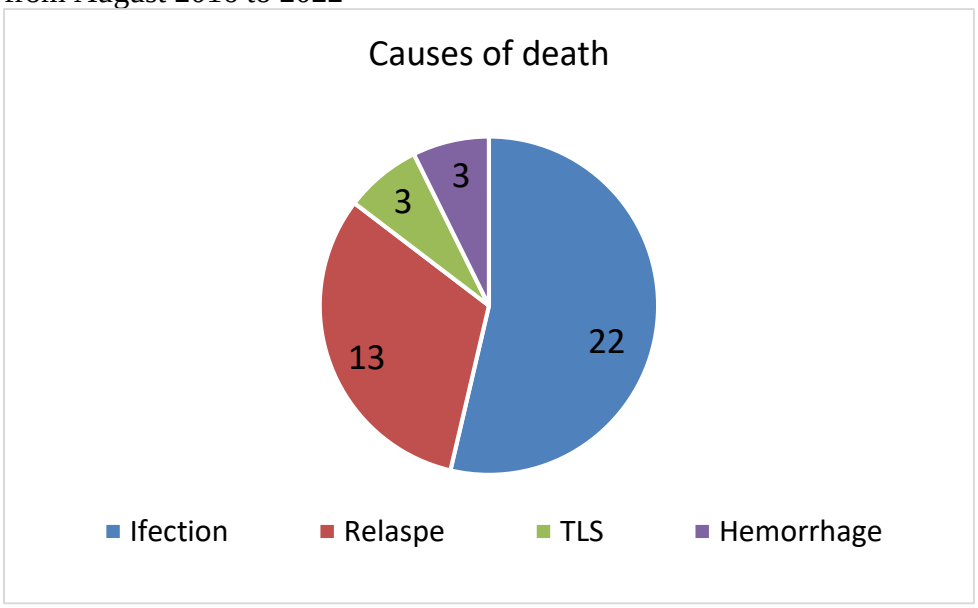
Among patients who started chemotherapy**,** 66(6.7%) of them completed induction, 50(50.5%) consolidation, 45(45%) interim maintenance, and 32(32.3%) delayed intensification. Only 8(8%) the patients who diagnosed with ALL completed their treatment successfully. There were 13(13.13%) relapses at different point course of their treatment, 2 of them were early relapse, and the rest were very early & 39(36.1%) of them abandon treatment after started chemotherapy.

There was a total of 41(37.9%) deaths. Sixteen (39% of the death were due to disease progression (3 patient hemorrhage, 11 with infection and 2 were AKI due to TLS), Thirteen (31.7%) of the deaths were due to relapse, and the rest 12(29.2%) were dead of treatment related complications (almost all dead from infection except one case by TLS complication). Four patients were dead before chemotherapy commencement with diseases progression, 8 died in prophase; 11 in induction 3 in maintenance by treatment related toxicity; and the rest two patients were died in D/intensification and consolidation. The rest 13 patients were dead from relapse at different cycle. Two patients were early relapse.

Table 4: Treatment status among pediatrics treated for ALL at JUMC-POU from August 2016 to 2022

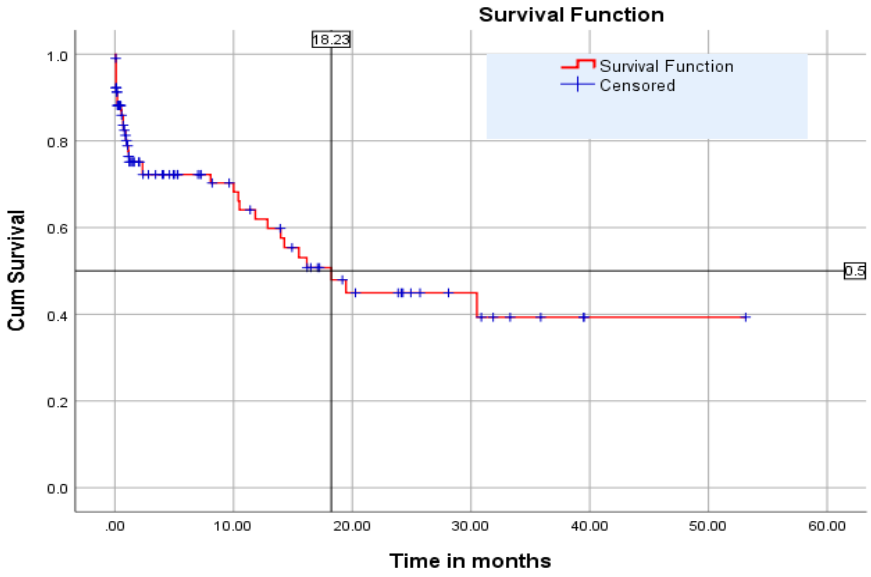
Treatment Status among admitted patients		
Status	Frequency	
	Number	Percentage
On treatment	18	16.7
Abandon treatment	39	36.1
Relapse	13	12
Dead	41	37.9
1. Relapse	13	12.2
2. Treatment related toxicities	12	11.3
3. Disease progression	16	14.8
Complete chemo and on follow up	8	7.4
Referred	2	1.8
Total	108	100.0

Figure 2: Immediate Causes of death among pediatrics admitted with ALL at JUMC-POU from August 2016 to 2022



Survival time was assessed from the day patients started chemotherapy to the last patient seen at our unit, which ranges from 02 days to 1250 days; the estimated median was 547.0± 102.3 days at 95% of CI. Three years probability of event free survival in this study was around 39%.

Graph A and B: Survival function and Hazard function in month among pediatrics admitted with ALL at JUMC-POU from August 2016 to 2022



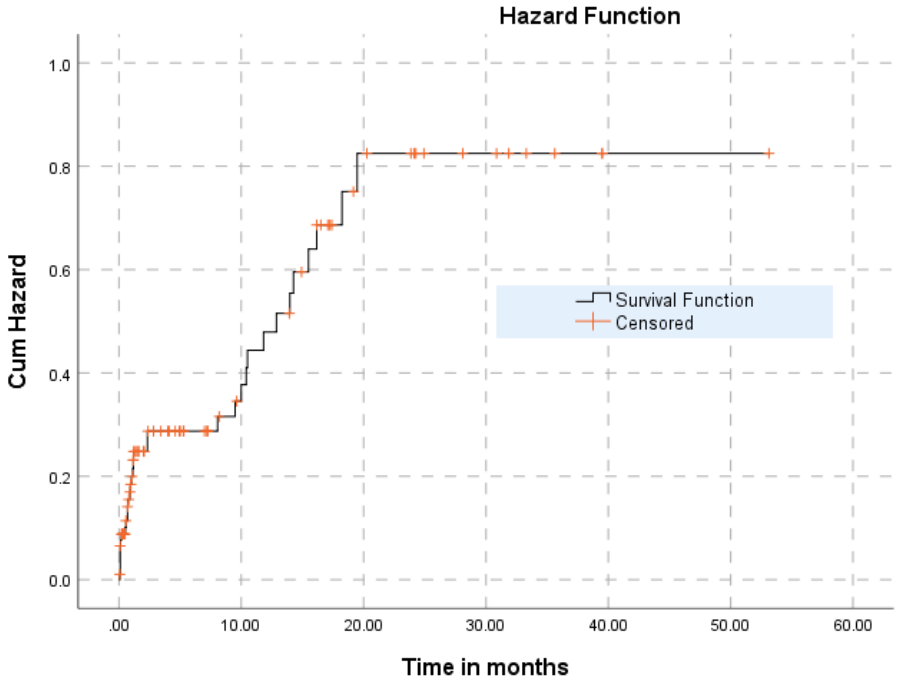


Table 5: Means and Medians time to events and overall survival among pediatrics admitted with ALL at JUMC-POU from August 2016 to 2022

Means and Medians time to events and overall survival.								
Event in months	Mean				Median			
	Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
Death	1.944	.815	.347	3.541	.700	.129	.448	.952
Relapse	11.162	1.667	7.894	14.429	11.830	1.480	8.929	14.731
Abandoned	4.157	1.018	2.161	6.152	1.330	.230	.879	1.781
Overall	26.079	3.074	20.054	32.104	16.170	2.909	10.468	21.872

Association

Cox regression was carried out to find the statistical association Time to acute lymphoblastic leukemia outcome and & related factors. By using a 95% confidence interval and $p<0.05$, multivariate analysis, it was found that WBC> 50,000 (p = .00) had significant association to early relapse or death compared to WBC <50,000. The White blood cell count > 50,000 had 3.60 times risk of relapse or death each month than those <50,000 patients.

Prognostic factors that had a statistically significant unfavorable impact on survival by univariate analysis were age < 1 year and WBC > 5000/micro letter. On multivariate even though it is not significant, the age range between 0 to 12 months had 1.33 times, & age >10 years had also 1.32 times likelihood of relapse or dying from ALL with each month; male had also 1.22 times more likelihood of relapse or death each month from ALL than females.

If there was correlation between hemoglobin or platelet value, distance from hospital, residence & nutritional statuses at first visit against time of outcome was calculated with Cox proportional hazards regression model, shows not significant.

Table 6: Cox proportional hazards regression model on time to outcome of ALL & association of variables

Variables in the Equation			
	Univariate analysis	Multivariate model	
	Crude HR (95.0% CI)	Adjusted HR (95.0% CI).	*P value*
Sex(male vs female)	1.56(.79-3.05)	1.222(.59-2.50)	.584
WBC (> 50000 vs <50,000)	3.84(1.99-742)	3.60(1.82-7.13)	.000
Age category			.710
Age (< 12 mo. Vs 1 - 9.9yr)	2.58(.59-11.34)	1.3359(.29-6.11)	.710
Age (>9.9. Vs 1 - 9.9yr	1.35(.70- 2.61)	1.318(.66-2.59)	.425

6. Discussion

Among patients treated for ALL, from August 2016 to 2022 GC, age range 0-12 month was 4 patients and age greater than or equal to ten years were 36 patients; generally with age 40 (40.8%) were high risk, higher than study done from Egypt (30%)[26]

The WBC count at presentation was > 50,000 in around 32(29.6%) patients which also suggests high risk, which is lower than study from Cambodia (48.2%), Tanzania (41%) and Egypt (39.6%)[26]–[28]

With combination of age (<12 mo. & 9.9 year), WBC, CNS status clinically and Chest X-ray evaluations among admitted patients 69(63.8%) were high risk which higher than study from Egypt (58.4%)[26]

In our study, cytochemistry, immunephenotyping, cytogenetic and molecular biology were no done, due to a lack of financial means and a local laboratory that could perform these examinations. Because diagnoses of leukemia were based on bone marrow or peripheral blood morphology alone, it was not possible to accurately differentiate between B and T cell progenitor ALL.

The median age of patients was 7.0 ± 4.3. years which is comparable that of institution hospital based retrospective study done at Malawi, but lower than that of Burkina Faso & higher than study done in Egypt as well as Turkey [23,24], [26].

There were slight male predominance which is similar with that of institutional based retrospective study done at Nigeria, Burkina Faso and Turkey[29] [11], [12], [22]

Outcome of ALL

This study shows that the induction remission among patients started chemotherapy was 67% which is higher than study done Malawi (55%), Burkina Faso(25%) [12], [14] [17]; it is comparable with induction remission reported from Mali (64%) [16]; however is lower than report from Turkey (97%)[11]. The Protocol used by Malawi was different that they did not have prophase and used cyclophosphamide in terms of L-ASP in induction; comparing to Burkina Faso also all patients were treated with standard risk protocol.

However relative to the Turkey, JUMC facility had no sophisticated investigation to sort the patients out in order to stratify risks, and select appropriate chemotherapy intensity.

The study also shows case fatality of ALL among pediatrics admitted to pediatric oncology unit was 37.9%, including those died from relapse, which is lower than retrospective hospital based study done in Malawi (45%), Mali (82%) & Burkina Faso (75%)[12], [14], [16]. The death rate from Malawi, Mali and Burkina Faso study was highier could be arised from protocol difference.

However, death in our setup is higher than that of Kenya (30%) & Turkey (20.1%)[11], [13]. Comparing to Turkey our facility higher mortality rate could explained by the late diagnosis, the difficulties of access to supportive care and the irregularity in the monitoring of treatment.

The commonest causes of death in ALL patients at JUMC facility was diseases progress and relapse each accounting 39% and 31.7% of death respectively. The common immediate causes of death at our setup was infection followed by relapse. This may indicate presence of gap on infection prevention and narrow ranges of antibiotic of choice for infection coverage in developing countries. The other problem in the facility at JUMC is lack of treatment for

relapse, except palliative care. More than half of death caused by non-relapse were occurred before chemotherapy initiation and in prophase which suggested patients were coming late and treatment associated complications as reported by many study from developing country. [11], [13], [15], [27].

Regarding to the relapse there were 13(13.1%) relapse at different treatment cycles is comparable with study done in Turkey (14.8%)[11] however, is lower than facility based study done in Malawi (25%)[14]. Comparing to Malawi there was protocol difference and the study period was also different whic may be risk for highier relapse. Except two patients the rest relapse was before eighteen months.

Three years event free survival in this study was around 39% better than Study done in Cambodia(34.9%) and Tanzania < 33% [28], [30], where higher abandonment because of financial; comparable with study done in Indonesia (40%)[31]. However, lower than study done in Brazil which was (57%), Egypt (69%), Turkey (76%), [26], [32], [33] This gap may arise from the quality of service, such as infection prevention & ICU care, or attendant awareness on treatment goal.

The study shows that rate of treatment abandonment, among started chemotherapy, was 36.1% is comparable with Indonesia (35%)[34]; higher than study done in Kenya (24%), Burkina Faso (12%), Mali (12%) [12]–[14]. The reason lower abandonment from Burkina Faso and Mali could be all drugs were given by NGO and their sample size was also smaller. In addition to these Mali patients were from city nearest to the hospital.

Our facility treatment completion was 8% which is almost similar studies from Africa: Malawi 10%, Tanzania 3.7%, and Nigeria- 5%[16], [22], [28]

Strength

The fact that the first research done on time to outcome of pediatrics ALL at JUMC facility, it gave a clue on possible limitations of ALL care which might be used as a stepping stone for revising treatment guideline: ALL, infection and other supportive care and for further prospective study aimed at identifying gaps on the treatment of ALL.

Limitation

Since this study conducted retrospectively, their completeness was difficult to check and some important data were missed. So, in this study not all prognostic and associated factors known to affect time to outcome were included.

Conclusion

WBC > 50000 at admission has significant poor prognostic factor for relapse or death.

The outcome of patients with acute lymphoblastic leukemia generally similar with most findings in the literature from developing country. However, it is lower when compared with studies from middle income and high-income countries. From patients visited JUMC and started treatment; around 67% patients completed induction achieve remission; 51% consolidation, 45% I/maintenance, 32.4% D/intensification and 7.5% patient completed treatment successfully. The 3 years EFS of our study was 39% which is comparable with those of Sub-Saharan countries.

Death and treatment abandonment were a major problem identified which makes low outcome at our setup. There was a very high early and induction mortality but comparable CR rates to most developing countries centers.

Recommendation

- ✓ Prospective collection of patient data to overcome missing information
- ✓ Strengthen the supportive care to avert preventable treatment and diseases related morbidities including: Infection, Hemorrhage, TLS, etc.
- ✓ Strengthen psychosocial support to avert treatment abandonment

Annex: I References

[1] Swerdlow SH, Campo E, Harris NL, et al, editors, 'WHO classification of tumours of haematopoietic and lymphoid tissues.', *IARCPress*, pp. 157–78, 2008.

[2] Bennett JM, Catovsky D, Daniel MT, et al., 'Proposals for classification ofthe acute leukemias. .. 1976; 33:451–458.', *Br J Haematol*, vol. 33, pp. 451–458, 1967.

[3] Bennett JM, Catovsky D, Daniel MT, et al., 'The morphological classification of acute lymphoblastic leukemia: Concordance among observers and clinical correlations.', vol. 47, pp. 552–561, 1998.

[4] M. Kato and A. Manabe, 'Treatment and biology of pediatric acute lymphoblastic leukemia', *Pediatrics International*, vol. 60, no. 1, pp. 4–12, Jan. 2018, doi: 10.1111/ped.13457.

[5] K. Horibe *et al.*, 'Incidence and survival rates of hematological malignancies in Japanese children and adolescents (2006–2010): based on registry data from the Japanese Society of Pediatric Hematology', *Int J Hematol*, vol. 98, no. 1, pp. 74–88, Jul. 2013, doi: 10.1007/s12185-013-1364-2.

[6] S. T. Memirie *et al.*, 'Estimates of Cancer Incidence in Ethiopia in 2015 Using Population-Based Registry Data', *JGO*, no. 4, pp. 1–11, Dec. 2018, doi: 10.1200/JGO.17.00175.

[7] S. P. Hunger and C. G. Mullighan, 'Acute Lymphoblastic Leukemia in Children', *N Engl J Med*, vol. 373, no. 16, pp. 1541–1552, Oct. 2015, doi: 10.1056/NEJMra1400972.

[8] M. M. Hudson, M. P. Link, J. V. Simone, and S. Consulting, 'Milestones in the Curability of Pediatric Cancers', *JOURNAL OF CLINICAL ONCOLOGY*, p. 8.

[9] K. Pritchard-Jones *et al.*, 'Sustaining innovation and improvement in the treatment of childhood cancer: lessons from high-income countries', *The Lancet Oncology*, vol. 14, no. 3, pp. e95–e103, Mar. 2013, doi: 10.1016/S1470-2045(13)70010-X.

[10] P. Farmer *et al.*, 'Expansion of cancer care and control in countries of low and middle income: a call to action', *The Lancet*, vol. 376, no. 9747, pp. 1186–1193, Oct. 2010, doi: 10.1016/S0140-6736(10)61152-X.

[11] V. Hazar, G. T. Karasu, V. Uygun, M. Akcan, A. Küpesiz, and A. Yesilipek, 'Childhood Acute Lymphoblastic Leukemia in Turkey: Factors Influencing Treatment and Outcome: A Single Center Experience', *Journal of Pediatric Hematology/Oncology*, vol. 32, no. 8, pp. e317–e322, Nov. 2010, doi: 10.1097/MPH.0b013e3181ed163c.

[12] S. Douamba, F. Diallo, and D. Yé, 'Acute lymphoblastic leukemias of children in Ouagadougou (Burkina Faso): results of management according to the protocol of the Franco-African Group of Pediatric Oncology 2005', p. 8.

[13] G. Olbara *et al.*, 'Childhood acute lymphoblastic leukemia treatment in an academic hospital in Kenya: Treatment outcomes and health-care providers' perspectives', *Pediatr Blood Cancer*, vol. 68, no. 12, Dec. 2021, doi: 10.1002/pbc.29366.

[14] G. Chagaluka *et al.*, 'Treating childhood acute lymphoblastic leukemia in Malawi', *Haematologica*, vol. 98, no. 1, pp. e1–e3, Jan. 2013, doi: 10.3324/haematol.2012.071985.

[15] S. Abdelmabood, A. E. Fouda, F. Boujettif, and A. Mansour, 'Treatment outcomes of children with acute lymphoblastic leukemia in a middle-income developing country: high mortalities, early relapses, and poor survival', *Jornal de Pediatria*, vol. 96, no. 1, pp. 108–116, Jan. 2020, doi: 10.1016/j.jped.2018.07.013.

[16] Togo B, 'Childhood acute lymphoblastic leukemia in sub– Saharan Africa: 4 years' experience the pediatric oncology unit Bamako, Mali. J Child Adolescent Health.', *2018*, vol. 2, no. 2, p. 246.

[17] S. Yifru and D. Muluye, 'Childhood cancer in Gondar University Hospital, Northwest Ethiopia', *BMC Res Notes*, vol. 8, no. 1, p. 474, Dec. 2015, doi: 10.1186/s13104-015-1440-1.

[18] C. Rodriguez-Galindo *et al.*, 'Toward the Cure of All Children With Cancer Through Collaborative Efforts: Pediatric Oncology As a Global Challenge', *JCO*, vol. 33, no. 27, pp. 3065–3073, Sep. 2015, doi: 10.1200/JCO.2014.60.6376.

[19] ‘Twinning Programs and Mentoring Relationships’, 2019, Accessed: May 10, 2022. [Online]. Available: (https://www.iceccancer.org/twinningprogramsoverview/)
[20] WHO, ‘Global initiative for childhood cancer. Updated 2 November 2020’, Nov. 2020, Accessed: May 03, 2022. [Online]. Available: www.who.int/docs/default source/a future for children/booklet.
[21] D. Hailu *et al.*, ‘Training pediatric hematologist/oncologists for capacity building in Ethiopia’, *Pediatr Blood Cancer*, vol. 67, no. 12, Dec. 2020, doi: 10.1002/pbc.28760.
[22] A. B. Oyesakin, V. E. Nwatah. et. al. ‘Pattern of childhood acute leukemia presentation at a tertiary hospital in Nigeria: a five-year review’, *Int J Contemp Pediatr*, vol. 5, no. 6, p. 2123, Oct. 2018, doi: 10.18203/2349-3291.ijcp20184202.
[23] F. Tzortzatou-Stathopoulou, et. al.‘Low Relapse Rate in Children With Acute Lymphoblastic Leukemia After Risk-Directed Therapy’:, *Journal of Pediatric Hematology/Oncology*, vol. 23, no. 9, pp. 591–597, Dec. 2001, doi: 10.1097/00043426-200112000-00008.
[24] M. S. Christensen *et al.*, ‘Treatment-related death in childhood acute lymphoblastic leukaemia in the Nordic countries: 1992-2001’, *Br J Haematol*, vol. 131, no. 1, pp. 50–58, Oct. 2005, doi: 10.1111/j.1365-2141.2005.05736.x.
[25] E. Glodkowska, A. Bialas, and T. Jackowska, ‘[Comparison of the present and previously used protocol of risk stratification in children with acute lymphoblastic leukemia]’, *Med Wieku Rozwoj*, vol. 11, no. 2 Pt 1, pp. 153–158, Jun. 2007.
[26] H. Hussein *et al.*, ‘Outcome and Prognostic Factors of Acute Lymphoblastic Leukemia in Children at the National Cancer Institute, Egypt’, *Journal of Pediatric Hematology/Oncology*, vol. 26, no. 8, pp. 507–514, Aug. 2004, doi: 10.1097/01.mph.0000132735.93396.92.
[27] L. Küpfer *et al.*, ‘Treatment of children with acute lymphoblastic leukemia in Cambodia’, *Pediatric Blood & Cancer*, vol. 68, no. 10, Oct. 2021, doi: 10.1002/pbc.29184.
[28] E. Kersten, P. Scanlan, S. G. DuBois, and K. K. Matthay, ‘Current treatment and outcome for childhood acute leukemia in Tanzania: Leukemia Outcome in Tanzania’, *Pediatr Blood Cancer*, vol. 60, no. 12, pp. 2047–2053, Dec. 2013, doi: 10.1002/pbc.24576.
[29] Mandal, Ananya., ‘“What is Acute Lymphoblastic Leukemia?”.’, *June 5, 2019*, News-Medical., pp. 1–3, 2019.
[30] C. Rodriguez-Galindo, P. Friedrich,et.al. ‘“Global challenges in pediatric oncology”, Current Opinion in Pediatrics’’, *Current Opinion in Pediatrics*, vol. 25, no. 1, pp. 3–15, Feb. 2013, doi: 10.1097/MOP.0b013e32835c1cbe.
[31] I. Purnama, P. H. Widjajanto, and W. Damayanti, ‘Influence of initial treatment delay on overall survival and event-free survival in childhood acute lymphoblastic leukemia’, *PI*, vol. 61, no. 4, pp. 217–22, Aug. 2021, doi: 10.14238/pi61.4.2021.217-22.
[32] T. A. Bonilha, D. D. A. Obadia. et al. ‘Outcome of childhood acute lymphoblastic leukemia treatment in a single center in Brazil: A survival analysis study’, *Cancer Reports*, vol. 5, no. 1, Jan. 2022, doi: 10.1002/cnr2.1452.
[33] C. Strahlendorf *et al.*, ‘Enrolling children with acute lymphoblastic leukaemia on a clinical trial improves event-free survival: a population-based study’, *Br J Cancer*, vol. 118, no. 5, pp. 744–749, Mar. 2018, doi: 10.1038/bjc.2017.462.
[34] S. Mostert, M. N. Sitaresmi, C. M. Gundy, Sutaryo, and A. J. P. Veerman, ‘Influence of Socioeconomic Status on Childhood Acute Lymphoblastic Leukemia Treatment in Indonesia’, *Pediatrics*, vol. 118, no. 6, pp. e1600–e1606, Dec. 2006, doi: 10.1542/peds.2005-3015.

Questionnaire Code_____ Date_____
Sign of DC _____ Sign of PI _____

The following variables were analyzed: gender, age, white blood-cell count, nutritional status and risk group on diagnosis; rates of remission and relapse, death and overall survival; place of relapse and risk factors for survival.

Annex II

Questionnaires

- A questionnaire prepared for collecting data for the study aiming to assess Time to outcome and associated factors among pediatrics treated for ALL the last six years at JMC, Jimma, South West Ethiopia from August, 2016 to August, 2022
- Dear Data collector

  There are multiple choice questions to be answered by making "encircle'' where indicated fill in the blank space.

A questionnaire prepared for collecting data for the study aiming to assess time to outcome of ALL and associated factors among children and adolescent treated for ALL the last six years at JMC, Jimma, South West Ethiopia from August, 2016 to August, 2022

Questionnaire Code_____ Date_____

Sign of DC _____ Sign of PI _____

Data collection protocol for the Study of Patients with Acute Leukemia (ALL) at the JUMC			
Code	Question	Response	Remark
1.	Study ID number:	_____	
2.	Card Number	_____	
3.	Date of Admission	__/____/_____	
Part I Socio Demographic Characteristics			
4.	Age(months)		
5.	Sex	1. Male 2. Female	
6.	Residence of care Givers	i. Urban ii. Rural	
7.	Religion of care giver	_____	
8.	Region	_____	
9.	Zone	_____	
10.	Woreda	_____	

11.	Estimated distance from JUMC (estimated from google)		_____KM			
Part II Anthropometric parameters						
12.	Weight		_____Kg			
13.	Height /length		_____cm			
14.	MUAC		_____			
15.	WFH		_____			
16.	W/A		_____			
17.	HFA		_____			
18.	BMI		_____			
Part III. Disease related information						
19.	Duration of illness (in days)		_____			
20.	Date of diagnosis		_____/_____/_____			
21.	Mode of diagnosis (Can be more than one answer)		0. PBS 1. BMA 2. Other……			
Laboratory & other findings at admission.						Remark
22.	WBC/micL		23.	Hgb		
24.	#Neutrophil		25.	Lymphocyte		
26.	Platelet		27.	Uric acid		
28.	Cr		29.	BUN		

30.	K +		31.	LDH		
32.	Na +		33.	Ca ++		
34.	HIV status		35.	CNS (blast)		
36.	Liver size		37.	Chest X ray.		
38.	Spleen size.		39.	Other (specify)		

Part IV: Treatment and out come			
40.	Was chemotherapy started?	0. Yes 1. No	
41.	If answer of #40 is No, what is the reason	0. Treatment refusal 1. Death before treatment commencement 2. lack of chemotherapy 3. others(mention)_____ 4. unknown reason	

For those patients started chemo. fill the following table					Remark	The code of chemo drugs used during In front of each phase
	Phase	Started date	End date	Drug used during each phase		A. Prednisolone B. Dexamethasone C. MXT(IV) D. MXT(IT) E. MXT(PO) F. Vincristine G. E Coli Asparaginase H. Cyclophosphamide I. Cytosine Arabinoside J. Hydrocortisone K. IT-Triple L. 6-Mercaptopurine M. Doxorubicin
42.	Prophase					
43.	Induction					
44.	Consolidation					
45.	Interim phase					
46.	Delayed int.					
47.	Maintenance.					

48. Was the patient developed complication during treatment 0 Yes 1. No			
49. If yes to question #47, which of the following complications? (Can be more than one answers)			
0. Neutropenic fever 1. Bleeding 2. TLS 3. Renal failure 4. Superior mediastinum syndrome		5. Liver failure 6. HAI 7. Mucositis 8. Dead 9. Other, specify_____	
50. Was there treatment interruption during courses of treatment?		0. Yes 1. No	
51. If # 47 is yes, reason for interruption? (It can be more than one response. Please put the cycle of interruption In front of each response	0. Neutropenia, _____ 1. Thrombocytopenia, ____ 2. Drug side effect, __ 3. Drug un-availability_____	4. Severe infection___ 5. Treatment Abandonment --- 6. Other (specify)_____	
52. What is the final status of the patient at the time of data collection?	0. Alive and on treatment, date last seen_____ 1. Abandon treatment, date last seen_____ 2. Relapsed; date of relapse Dx_____ 3. Dead, date of death _____ 4. Completed treatment and on follow up; date last seen_____ 5. Other, specify_____ 6. Unknown		
53. If the patient is alive Phase of treatment during data collection ……			
54.	If the patient died, please fill the following table!		Remark.
	Condition related to treatment response during death	Phase Rx at death	Place (home/ JMC/ local hospital)

	0. Disease progression			
	1. Relapse while on treatment			
	2. Relapse after abandonment			
	3. Treatment related complication			
	4. Other (mention)			
	5. Unknown			
55.	What was the possible causes/s of death?			
	0. Neutropenic fever	1. Non-neutropenic sepsis		
	2. Typhlitis	3. Leukostasis		
	4. Haemorrhage	5. Other (mention)_____		
	6. TLS	7. Unknown		

Name of data Collector _____

Signature _____

Date_____