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Time to Diagnosis, Referral, and the Treatment Outcomes of Pediatric Patients with Acute Lymphoblastic Leukemia in a Tertiary Referral Center in Northern Luzon, Philippines

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ABSTRACT: Acute lymphoblastic leukemia (ALL) remains the most common pediatric hematologic malignancy and a major cause of cancer-related death in low- and middle-income countries. In the Philippines, despite health policies such as the National Integrated Cancer Control Act and the Universal Health Care Act, survival outcomes remain suboptimal, partly due to delays in diagnosis and treatment initiation. This study examined the time from symptom onset to diagnosis, referral, and therapy, and their association with clinical outcomes among pediatric ALL patients in a tertiary referral center in Northern Luzon. A descriptive cross-sectional review was conducted on 66 pediatric patients newly diagnosed with ALL and admitted to Baguio General Hospital and Medical Center between 2017 and 2024. Pre-diagnostic symptomatic interval (PSI), pre-treatment interval (PTI), and outcomes including remission, relapse, abandonment, overall survival (OS), and disease-free survival (DFS) were analyzed using descriptive statistics and Kaplan-Meier estimates. Most patients were male (62%) and aged one to nine years (71%). B-cell ALL comprised 41% of cases, T-cell 17%, and not otherwise specified (NOS) 42%. B-cell ALL had the longest median PSI at 21 days, while T-cell ALL was shortest at 7 days; NOS cases had the longest PTI at 9.25 days. Overall remission was 51.5%, highest among B-cell ALL (66.7%). Treatment abandonment was significantly greater in NOS cases (28.6%, $p<0.001$). The three-year OS was 71.2% and plateaued through seven years, while six-year DFS reached 51.5%, with B-cell ALL showing the best outcomes. Despite shorter delays compared with other resource-limited settings, survival remained below high-income benchmarks. Improving early detection, risk-based stratification, and patient navigation may help reduce abandonment and enhance survival.

KEYWORDS: Acute Lymphoblastic Leukemia, Pre-diagnostic symptomatic interval, Pre-Treatment Interval, Diagnosis Delay

I. INTRODUCTION

Acute lymphoblastic leukemia (ALL) is an aberrant blood cancer marked by the abnormal multiplication of immature lymphoid precursors in the bone marrow, circulating blood, and other body tissues. Pediatric acute leukemia constitutes around 77% of all cases, making it the predominant hematologic pediatric cancer.

The worldwide occurrence rate of childhood acute lymphoblastic leukemia (ALL) is approximately 4.32 per 100,000 children (Garnish D et al 2022). In Southeast Asia, the frequency rate reached 4.58 per 100,000 children in 2021 (Hu Y et al 2024). In the Philippines a total of 47,684 cases diagnosed with ALL from 2015-2024 based on the 10-year database from the Philippine Pediatric Society Disease registry. From 1990 to 2021, middle socio-demographic index regions showed an increasing trend in the estimated annual percentage change of the incidence rate (1.49) (Hu Y et al., 2024). The survival rate for kids with ALL from resource – limited nations, such as the Philippines, is lower (ranging from 50-70%) compared to high-income countries (90%). "Although the National Integrated Cancer Control Act (NICCA) and the Universal Health Coverage (UHC) Act of 2019 have been implemented in the Philippines, acute leukemia continues to cause substantial mortality, with approximately 1,700 deaths reported each year (WHO, 2021). These figures focus the crucial need to strengthen early finding, improve action protocols, and expand healthcare access, particularly in rural and underserved regions.

Barriers such as delays in diagnosis, limited referral systems, and the high cost or inaccessibility of treatment contribute to poor outcomes (WHO, 2021; Sampagar et al., 2023; Elhabashy et al., 2023). These challenges feature the urgent need to identify and implement alternative strategies for early detection and timely intervention. One critical area that remains insufficiently studied is the duration from symptom onset to referral, initiation of chemotherapy, and its correlation with treatment outcomes. This study aims to investigate these time intervals and evaluate their impact on the clinical outcomes of pediatric ALL patients. The

findings will serve as a foundation for developing a regionally appropriate patient navigation and referral system to improve survival rates and overall quality of care. This investigation seeks to evaluate the duration from initial symptom presentation to definitive diagnosis and commencement of treatment., as well as the outcome of pediatric patients with ALL from January 1, 2017, to December 31, 2024, referred to or registered at Baguio General Hospital and Medical Center.

Specifically, the study also intends to determine the following:

1. To identify the clinico-demographic profile of pediatric patients with Acute Lymphoblastic Leukemia referred to the Pediatric Hematology and Oncology Service of Baguio General Hospital and Medical Center in terms of:

1.1 Age upon diagnosis

1.2 Sex

1.3 Place of Origin

1.4 NCI Risk Stratification (High Risk and Standard Risk)

1.5 Immunophenotype (B cell ALL, T cell ALL, ALL Not otherwise specified (NOS)

2. To calculate the Pre-diagnostic symptomatic interval and Pre-Treatment interval of pediatric patients with ALL categorized by immunophenotype based on the following:

2.1. Pre-diagnostic Symptomatic Interval (PSI): duration from the symptom appeared to the time of diagnosis

2.1.1. PSI 1: the time interval from symptom onset to first physician consult or admission

2.1.2. PSI 2: the time interval from the first physician consult or admission to referral to hematologist with a clinical impression of Acute Leukemia

2.2. Pre-Treatment Interval (PTI): is the time between a diagnosis and the of the first treatment

2.2.1. PTI 1: the time interval from referral to a pediatric hematologist to the time of diagnosis

2.2.2. PTI 2: the duration from the time of diagnosis to the initiation of treatment (chemotherapy)

3. To identify the treatment of patient outcomes with ALL, categorized by immunophenotype, who were diagnosed from January 1, 2017, to December 31, 2024:

3.2.1 Remission

3.2.2 Induction Failure

3.2.3 Relapse

3.2.4 Lost-to-follow up

3.2.5 Abandonment of Treatment

3.2.6 Overall Survival

3.2.7 Disease-Free Survival

4. To identify the mean over-all survival and disease-free survival time in months among the immunophenotypes (B-ALL, T-ALL, ALL-NOS).

II. METHODOLOGY

This descriptive cross-sectional study used total enumeration to include all eligible participants. The participants (n=91) were based on the eight-year institutional database of BGHMC, which only include pediatric patients, newly born to 18 years of age, referred to and/or admitted in BGHMC from January 1, 2017, to December 31, 2024, with a final diagnosis of Acute Lymphoblastic Leukemia, and managed through chemotherapy. Patients who were referred to and transferred to a different institution, patients who have started chemotherapy from another institution, refused to initiate chemotherapy, charts with incomplete records of needed variables, and patients with comorbidities and synchronous malignancies were excluded (n=25). Thus, an overall 66 pediatric patients were involved in this study. Data was obtained from the patient's medical chart, both written and online via EMR. These include the (1) clinic-demographic profiles, (2) patient's history to identify the time of symptom onset, (3) dates when the following laboratory tests were done, as bases for the time of diagnosis: complete blood count, peripheral blood smear, bone marrow aspiration morphology and/ or flow cytometry results, and specialized tests such as Fluorescence In Situ Hybridization (FISH) for BCR/ABL1 tests. Dates or timing of symptoms to first consult, to referral to hematology-oncology service, to the initiation of treatment were noted from the medical records, both from OPD and In-patient records, to determine the time interval in days. Treatment outcomes were also determined in terms of remission, induction failure, relapses, loss to follow-up, abandonment of treatment, as well as the overall longevity and disease-free survival rate.

The principal investigator collected the data and were recorded on a standardized data collection sheet and subsequently encoded into a password secured spreadsheet available only to the principal researcher and the supervising investigator. All data

were encoded in Microsoft Excel and analyzed using IBM SPSS Statistics version 22.0. Descriptive statistics using mean and standard deviation or median for quantitative variables (demographic and clinical characteristics), and frequency and percentage for categorical variables such as the treatment outcomes of pediatric patients with ALL. The overall survival rate (OSR) and event-free survival (EFSR) rates at five years were computed using the Kaplan-Meier estimator. Data collected for the OS and EFS includes the time serial yearly, status (alive, mortality, events like relapse, abandonment until the end of the study period which were collated and subjected to analysis. The study was authorized by the Ethics Committee of Baguio General Hospital and Medical Center. All printed or written materials will be disposed, and digital files will be securely erased after five years. The study strictly complied with the Data Privacy Act of 2012 and Good Clinical Practice (GCP) guidelines. Furthermore, the Researcher has no financial or organizational ties and there will be no compensation needed. Hence, there is no conflict of interest.

III. RESULTS AND DISCUSSIONS

Demographics, Diagnostic Intervals, and Treatment Outcomes of Pediatric ALL Patients

Characteristic	Overall	B-cell ALL	T-cell ALL	ALL NOS
Patients, n (%)	66 (100)	27 (40.9)	11 (16.7)	28 (42.4)
Male sex, n (%)	41 (62.1)	16 (59.3)	7 (63.6)	18 (64.3)
Age 1–9 y, n (%)	47 (71.2)	21 (77.8)	8 (72.7)	18 (64.3)
Standard risk, n (%)	40 (60.6)	18 (66.7)	6 (54.5)	16 (57.1)
Median PSI, days (IQR)	15 (20.5)	21 (46)	7 (8.5)	14.8 (22.5)
Median PTI, days (IQR)	7.8 (12)	7.5 (21)	3.5 (3.5)	9.3 (8)
Remission, n (%)	34 (51.5)	18 (66.7)	7 (63.6)	9 (32.1)
Relapse, n (%)	4 (6.1)	3 (11.1)	0	1 (3.6)
Induction failure, n (%)	1 (1.5)	0	0	1 (3.6)
Treatment abandonment, n (%)	8 (12.1)	0	0	8 (28.6)*
Mortality, n (%)	19 (28.8)	6 (22.2)	4 (36.4)	9 (32.1)
3-year OS, %	71.2	77.8	36.4	67.9
6-year DFS, %	51.5	66.7	54.6	35.7

*PSI = pre-diagnostic symptomatic interval; PTI = pre-treatment interval; OS = overall survival; DFS = disease-free survival; NOS = not otherwise specified. *Treatment abandonment significantly higher in NOS group (p<0.001).*

Sixty-six pediatric patients with acute lymphoblastic leukemia (ALL) were analyzed. Most were male (62.1%) and between one and nine years old (71.2%). B-cell ALL accounted for 40.9% of cases, T-cell for 16.7%, and not otherwise specified (NOS) for 42.4%. A majority of patients were classified as standard risk (60.6%). The median pre-diagnostic symptomatic interval (PSI) was longest among B-cell ALL at 21 days compared with seven days for T-cell ALL and 14.8 days for NOS. The median pre-treatment interval (PTI) was shortest in T-cell ALL at 3.5 days and longest in NOS at 9.3 days, with the overall time from symptom onset to initiation of chemotherapy having a median of 25 days.

Treatment outcomes showed that 51.5% of patients achieved remission, with the highest rates among those with B-cell ALL (66.7%) and the lowest among NOS (32.1%). Relapse occurred in 6.1% of patients, and induction failure in 1.5%. Treatment abandonment was markedly higher among NOS cases at 28.6% ($p<0.001$). Mortality reached 28.8% overall, with the highest proportion in T-cell ALL (36.4%). Survival analysis demonstrated a three-year overall survival (OS) of 71.2%, which plateaued and remained stable through seven years. Disease-free survival (DFS) improved over time, from 16.7% at one year to 51.5% at six to seven years, with B-cell ALL achieving the most favorable long-term DFS at 66.7%.

Although diagnostic and treatment delays were shorter than those reported in many low- and middle-income countries, survival outcomes remained below those achieved in high-income settings, where advanced immunophenotyping, genetic profiling, and targeted therapies have led to cure rates exceeding 85–90%. The high proportion of NOS classification reflects diagnostic limitations and restricted access to comprehensive flow cytometry, while treatment abandonment remains a major barrier to improved outcomes. These findings indicate that earlier recognition and faster referral alone are insufficient to enhance survival. Broader access to accurate risk stratification, expanded diagnostic capacity, strengthened patient navigation, and socioeconomic support to reduce abandonment are essential steps to narrow the survival gap for pediatric ALL in resource-limited settings.

IV. CONCLUSIONS AND RECOMMENDATIONS

Analysis of a cohort of 66 pediatric ALL patients, predominantly males, aged 1-9, revealed that B-cell ALL patients experienced the longest pre-diagnostic intervals, while the NOS ALL group faced the most prolonged pre-treatment delays and a significantly higher rate of treatment abandonment (50%). Survival outcomes also varied by immunophenotype, with B-cell ALL showing the most favorable long-term survival rates and T-cell ALL demonstrating the poorest. Aside from immunophenotype, NCI risk stratification was a significant predictor of overall survival. Furthermore, pre-diagnostic and pre-treatment intervals in this cohort were found to be shorter compared to those in other middle-income countries, these reductions did not significantly improve clinical outcomes, which remained comparable to those recorded in other low- and middle-income countries. However, when analyzed in relation to high-income countries, which benefit from readily accessible immunophenotyping, genetic testing, and targeted therapies, the overall and disease-free survival rates in our study were significantly poorer.

Based on these findings, future research should prioritize identifying the determinants underlying the disproportionately high rate of treatment abandonment in the pediatric ALL cohort. A mixed-methods design is warranted to elucidate the socio-economic, psychological, and logistical barriers faced by families in resource-limited settings. National-level investigations are needed to quantify diagnostic and treatment delays, particularly in high-incidence regions, and to include larger, more representative samples to enhance generalizability. Longitudinal studies should also assess survival and quality-of-life outcomes among patients with non-adherence or delays compared to those completing protocols. The resulting evidence will be pivotal in guiding targeted, evidence-based interventions and policy reforms to strengthen patient navigation, improve treatment adherence, and optimize survival outcomes.

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