# SURVIVAL OF FILIPINO CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA DIAGNOSED IN A TERTIARY REFERRAL CENTER FOR CHILDHOOD CANCER: A RETROSPECTIVE COHORT STUDY

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**ABSTRACT**

**BACKGROUND:** Acute lymphoblastic leukemia (ALL) represents the largest group of pediatric malignancies. The high cure rate of childhood ALL represents one of the most remarkable success stories in the war against cancer. In a lower middle income country (LMIC) like the Philippines, we reviewed the 5-year survival in a tertiary referral center.

**OBJECTIVES:** This study aims to determine the 5-year survival of childhood ALL at a tertiary referral center for childhood cancer.

**METHODOLOGY:** Medical charts of newly diagnosed ALL ages 1 to 18 years old from January 2012 to December 2016 were reviewed.

**OUTCOME:** A total of 435 subjects were included in the study. The 5-year overall survival (OS) and event free survival (EFS) were 65.3% and 62.8%, respectively. The 5-year OS for standard risk ALL was 68.8% and for high risk ALL was 50%. The 5-year OS for the remission group was 83.7% and for the relapse was 21.1%. Univariate and multivariate analysis showed that WBC count at diagnosis, risk classification, immunophenotyping, and relapse showed significant prognostic impact for mortality.

**CONCLUSION:** The 5-year OS and EFS were lower compared to developed countries but are comparable with other LMICs. The prognostic factors for relapse and mortality were compatible with the literature. Overall, the adopted treatment protocols for childhood ALL in this institution showed acceptable results.

**KEY WORDS:** Childhood *Acute Lymphoblastic Leukemia, Filipino, Overall survival, Event Free Survival*

## INTRODUCTION

The 5-year event-free survival for childhood cancer is 75% to 79% in high-income countries (HIC). However, 80% of the world's children live in middle- and low-income countries (MIC and LIC), where poverty, lack of public health infrastructure, high mortality rates, and low childhood cancer cure rates are pervasive.[1] Various phenomena accounts for this survival gap, including treatment toxicity, higher rates of relapse and abandonment of therapy in LIC.[2]

Acute lymphoblastic leukemia (ALL) is the most common pediatric cancer, accounting for a quarter of all childhood malignancies. This potentially catastrophic disease was once fatal in four-fifths of patients, but the clinical outcome has improved remarkably over the past 50 years.[3] ALL is characterized by the clonal proliferation and accumulation of malignant blast cells in the bone marrow and peripheral blood.[4] These abnormal cells are arrested in the lymphoblast stage of the normal maturation pathway. Aberrations in proliferation and differentiation of these cells are common and normal hematopoiesis is suppressed. Symptoms result from varying degrees of anemia, neutropenia, and thrombocytopenia or from infiltration of the blast cells into tissues.[5]

Data from the Philippine Cancer Society–Manila Cancer Registry (PCS–MCR) and the Department of Health–Rizal Cancer Registry (DOH–RCR) from 2001-2005 showed an overall absolute survival of 32.3% for childhood ALL.[6] In 2003 to 2007, local data from a tertiary referral pediatric center, the Philippine Children's Medical Center showed the overall survival (OS) is 82%.[7] Currently, with the use of intensive chemotherapy and with increase in the support therapies such as blood transfusions and antibiotic therapy, around 70 to 75% of affected children can be cured with present treatment protocols.[8]

The high cure rate of children with ALL represents one of the most remarkable success stories in the war on cancer. Many factors have led to this high cure rate, including: (1) the use of combination chemotherapy, (2) presymptomatic treatment of the central nervous system, a sanctuary site, and, more recently, (3) the use of intensified therapeutic regimens. These major advances have been derived empirically through carefully controlled, randomized multi-institutional clinical trials.[9] One of the most well-known protocols for childhood ALL internationally was developed by the German Berlin-Frankfurt-Münster (BFM) group.[10] The primary objective of the treatment is to induce complete remission. The German-Swiss-Austrian study group responsible for BFM 90, published that disease free survival for six years 6 years (±SE) was 78±1% among the 2,178 patients studied.[11] Local Study done from 2005 to 2009 by Dujua et.al. at the University of Santo Tomas Hospital using the Modified Berlin-Frankfurt-Münster/Hong Kong Acute Lymphoblastic Leukemia (BFM95-HKALL97) protocol in 78 patients showed five-year OS and event free survival (EFS) rates were 86.94 % and 86.2%, respectively.[12] In a study at the Philippine Children's Medical Center from 2003 to 2007 in 111 patients by Galano et.al. showed OS of 82% at five years, for standard risk ALL given the modified BFM protocol OS showed 84.4% at five years, and for high risk ALL given CCG 1961 protocol OS was at 77.8% at five years.[7]

Although most children with acute lymphoblastic leukemia (ALL) are cured, certain subsets have a high risk of relapse.[13] Identification of groups at variable risk of relapse is done primarily to be able to inform modifications of therapy to limit short-term and long-term toxicities to those with more easily treatable disease and to intensify therapy for those with a worse prognosis. Improvement in outcome for higher-risk patients to date can largely be attributed to intensification of conventional chemotherapy.[14] The reported outcomes by the Children's Cancer Group (CCG) 1961 trial in three time periods, 1983–1988, 1989–1995, 1996–2002 and over the three intervals showed 10-year event-free survival (EFS) for Rome/NCI standard risk and higher risk B-precursor patients was 68% and 58%, 77% and 63%, and 78% and 67%.[15] Hence, our institution has adopted this protocol for the treatment high risk (HR) ALL.

Even with the risk-stratified and more intensive frontline therapy, 20-25% of children with ALL still relapse. The treatment of patients with relapse ALL remains unsatisfactory, with suboptimal re-induction remission rates and poor long-term overall survival rates ranging from 15-50%. We have adopted the Memorial Sloan-Kettering-New York II (MSK-NY-II) protocol for the ALL with relapse to the bone marrow or extramedullary (testicles or CNS) or a combined marrow and extramedullary relapse. Pilot study of the MSK-NY-II protocol showed in a median follow-up of 54+ months, the event-free survival (EFS) rate was 86%±10%. Disease-free survival (DFS) rate at 48 months was 93%. The estimated 4-year EFS rates for the high-risk and average-risk patients were 83±14% and 93 **%** respectively.[16]

The advent of intrathecal therapy as CNS prophylaxis has changed the paradigm of ALL treatment and has remarkably decrease cases of meningeal leukemia. This was further enhanced with systemic therapy using high dose methotrexate. However, a large number of patients at would still develop relapses, which usually is isolated to extramedullary sites, most commonly in the CNS, testicular, or ocular locations.[17] The treatment philosophy of intensive systemic therapy with anti-leukemic drugs that penetrate the CNS plus delayed CNS radiation used by Pediatric Oncology Group (POG), has resulted in significant improvements in outcome for patients with isolated CNS relapse of ALL. Previously, most studies had reported EFS rates below 50%. This shift in treatment philosophy resulted from the realization that most failures after isolated CNS relapse occurred in the bone marrow. Therefore, POG designed a regimen that intensified systemic therapy for 12 months while delaying radiation. The overall 4-year event-free survival (EFS) of the POG 9412 trial for the precursor B-cell patients with CNS relapse is at 70.1%±5.8%.[18] With the improvement in the survival using POG 9412 trial for isolated CNS relapse, we have adopted this protocol in our setting.

The management of ALL has drastically changed over the years and numerous protocols had been developed both for high income and low income countries. Treatment is optimally tailored to each individual patient's risk of failure so that chances for cure can be maximized, while unnecessary toxicity can be avoided.[14] With the application of these international protocols to our setting, this study was conducted to review the overall survival rate at our institution to assess the effectiveness of application of such protocols among our patients.

## OBJECTIVES

### General Objective

The general objective is to determine the survival of children 1-18 years old with acute lymphoblastic leukemia treated at a tertiary referral center for children from January 2012 to December 2016.

### Specific Objectives

1. To describe the demographic and clinical characteristics of children diagnosed with ALL based on Rome/NCI Criteria, as to: a) age b) sex c) geographic region d) initial white cell count e) initial CNS status f) remission status post-induction g) FAB morphology/immunophenotype

2. To determine the overall survival (OS) and event free survival (EFS)

3. To determine the proportion of post-induction remission failure and relapse

4. To describe the sites of relapse and time to relapse (whether less than 18 months or more than 18 months) from diagnosis

5. To identify the causes of death

6. To assess the associated risk between treatment outcomes with risk classification and occurrence of relapse and mortality

## METHODOLOGY AND STATISTICAL ANALYSIS

This was a retrospective cohort study conducted at the Philippine Children's Medical Center from January 2012 to December 2016.

Approval by the Philippine Children's Medical Center Institutional Review Board was obtained for this retrospective analysis. Medical Charts (in-patient and out-patient) of the patients newly diagnosed with ALL age 1 to 18 years old who underwent treatment at the Philippine Children's Medical Center from January 2012 to December 2016 were reviewed.

The following data were collected: demographic characteristics (age, sex, and geographic location), criteria based on Rome/NCI Criteria: a) initial white cell count b) initial CNS status c) status post-induction (whether remission or failure) d) FAB morphology/immunophenotype; the proportion of remission failure, relapse (time to relapse from diagnosis whether less than 18 months and more than 18 months, sites of relapse), and the cause of death.

The primary outcomes of 5-year OS and EFS among children ages 1-18 years old newly diagnosed with ALL standard risk treated with a modified version of the Berlin-Frankfurt-Münster/Hong Kong Acute Lymphoblastic Leukemia (BFM95/HKALL97) protocol, ALL high risk treated with Children's Cancer Group CCG 1961, and ALL relapse patients treated with Memorial Sloan Kettering New York MSK NY II protocol or Isolated CNS relapse Children's Oncology Group POG 9421 were determined.

The associated hazards between treatment outcomes with clinical profile and occurrence of mortality were also evaluated.

ALL is diagnosed when 25% lymphoblasts or more in the bone marrow aspirate will be present using FAB classification or using immunophenotyping (flowcytometry). Cytogenetics by karyotyping was not done on all our patients due to the high cost of the test and unavailability at our institution. Cerebrospinal fluid analysis was done on all patients for staging. Minimal residual disease evaluation was done at the end of induction phase 1A by flowcytometry.

Details of the treatment protocols are provided in the appendix. In the BFM95/HKALL97 protocol, the first part of induction chemotherapy comprised of four drugs and lasted 5 weeks. The second part comprised of 4 weeks of cytarabine arabinoside with intrathecal chemotherapy and 2 doses of high-dose cyclophosphamide. The consolidation phase included four 2-weekly courses of high-dose methotrexate (1 $g/m^2$). The delayed intensification commenced at week 22 after diagnosis (re-induction phase). Reinduction further enhanced treatment outcome, suggesting that the increased dose-intensity of other drugs—such as asparaginase—led to the noted improvement.[19] Daily mercaptopurine and methotrexate every week constitute the backbone of continuation regimens for the maintenance therapy.[20]

The ALL patients classified under high risk category were given the CCG 1961 protocol. Children with high-risk are treated with four or more drugs for remission induction for a more intensified regimen.[19] If marrow blasts remain $\geq$5% at the end of consolidation or patients experienced relapse during treatment, Memorial Sloan Kettering New York MSK NY II protocol were instead given. For those who developed isolated CNS relapse, they were shifted to isolated CNS relapse POG 9461 protocol.

Trimethoprim-sulfamethoxazole combination was given to all patients twice daily for three days per week from the start of the chemotherapy treatment up to three months after completion of chemotherapy as prophylaxis against *Pneumocystis jerovici* pneumonia.

Bone marrow response was evaluated at the end of induction phase 1A. Complete remission (CR) was defined as less than 5% blasts in the bone marrow by flowcytometry or BMA status of M1 by morphology, the absence of leukemic blasts in blood and CSF, and no evidence of localized disease. Resistance to therapy (remission failure) was defined as not having achieved complete response by the end of the induction phase. Relapse was defined as recurrence of 25% or more lymphoblasts in the bone marrow and/or localized leukemic infiltrates at any site.

Statistical methods employed were summary statistics (means, SD, frequency, percentages) for socio-demographic information and clinical characteristics. The Kaplan-Meier survival analysis was used to estimate EFS and OS. Censored observations were included and applied to the patients who abandoned treatment and to the group still alive and event-free. Univariate and multivaraite analysis was done using Cox regression proportional hazard.

## RESULTS

A total of four hundred and forty seven medical charts were reviewed. Four hundred and thirty five patients were included in the study, twelve patients were excluded, of which six were infantile type of leukemia (age less than 1 year old) and the other six were failure of induction. Table 1 shows the demographic and clinical characteristics of the subjects. The mean age at diagnosis was at 6.6 years ± 4.3 standard deviation. There were more boys than girls at a ratio of 1.4:1. Majority of the patients were categorized under standard risk ALL at 60.7% of the total subjects and 39.3% were high risk ALL. Initial white blood cell count at diagnosis has a mean of 43.16 (0.5 - 502.3) x $10^9$/L. According to immunophenotyping, the greater proportion of the population were Pre-B cell ALL at 88.3%, followed by T-cell ALL at 10.6%, biphenotypic 0.9%, and mature B cell 0.2%. CNS status on diagnosis showed CNS involvement in only 1.8% of the population. Failure of induction was seen in 6 out of 447 total patients at 1.3%. Overall outcome showed 63.7% live patients, 16.8% abandonment, and 19.5% dead. This illustrates an overall remission rate of 80.9% at the time of data collection and 19.1% developed relapse. For the duration from diagnosis to relapse, the group who developed early relapse (less than 18 months) showed 54.2% while the group who developed late relapse (more than 18 months) was 45.8%. The duration from relapse to death showed mean of 244.6 (38 – 527) days. As to the status of the relapse group, 7.2% had completed treatment and presently in remission, 63.9% deaths, the 27.7% were currently on-going treatment and in remission, and 1.2% on oral metronomics therapy. The causes of death reported showed majority died from septic shock 63.5%

**Table 1.** Clinical Profile of the patients with Acute Lymphoblastic Leukemia diagnosed at Philippine Children's Medical Center Cancer and Hematology Center from January 2012- December 2016

| Characteristic | All population (N = 435) | Standard Risk Group (N = 264) | High Risk Group (N = 171) |
|---|---|---|---|
| | Frequency (%); Median (range); Mean ± SD | Frequency (%); Median (range); Mean ± SD | Frequency (%); Median (range); Mean ± SD |
| **Age (years)** | 6.6 ± 4.3 | 5 ± 2.4 | 9.5 ± 4.8 |
| Age 1-10 years old | 340 (78.2) | | |
| Age >10 years old | 95 (21.8) | | |
| **Sex** | | | |
| Male | 257 (59.1) | 143 (54.2) | 114 (66.7) |
| Female | 178 (40.9) | 121 (45.8) | 57 (33.3) |
| **Locality** | | | |
| Region 1 | 14 (3.2) | 9 (3.4) | 5 (2.9) |
| Region 2 | 5 (1.3) | 4 (1.5) | 1 (0.6) |
| Region 3 | 84 (19.3) | 52 (19.7) | 32 (18.7) |
| Region 4 | 114 (26.2) | 62 (23.5) | 52 (30.4) |
| Region 5 | 22 (5.1) | 13 (4.9) | 9 (5.3) |
| Region 6 | 5 (1.1) | 2 (0.8) | 3 (1.6) |
| Region 7 | 4 (0.9) | 3 (1.1) | 1 (0.6) |
| Region 8 | 6 (1.4) | 2 (0.8) | 4 (2.3) |

| Characteristic | All population (N = 435) | Standard Risk Group (N = 264) | High Risk Group (N = 171) |
|---|---|---|---|
| | Frequency (%); Median (range); Mean ± SD | Frequency (%); Median (range); Mean ± SD | Frequency (%); Median (range); Mean ± SD |
| Region 9 | 1 (0.2) | 1 (0.4) | - |
| CAR | 2 (0.5) | 1 (0.4) | 1 (0.6) |
| NCR | 178 (40.9) | 115 (43.6) | 63 (36.8) |
| **Risk Classification** | | | |
| Standard Risk | 264 (60.7) | | |
| High Risk | 171 (39.3) | | |
| **White Blood Cell Count ( x $10^9$/L)** | 43.16 (0.5 – 502.3) | 11.9 (0.8 – 49.4) | 63.61 (0.5 – 502.3) |
| **Immunophenotyping** | | | |
| Pre-B Cell ALL | 384 (88.3) | | |
| T-Cell ALL | 46 (10.6) | | |
| Mature B Cell | 1 (0.2) | | |
| ALL Biphenotypic | 4 (0.9) | | |
| **CNS Status on Diagnosis** | | | |
| CNS 1 | 401 (92.2) | 252 (95.5) | 149 (87.1) |
| CNS 2 | 1 (0.2) | - | 1 (0.6) |
| CNS 3 | 7 (1.6) | - | 7 (4.1) |
| Not done | 26 (6.0) | 12 (4.5) | 14 (8.2) |
| **Bone Marrow status Post-Induction** | | | |
| Remission (M1 marrow) | 401 (92.2) | 251 (95.0) | 150 (87.7) |
| Not done | 34 (7.8) | 13 (4.9) | 21 (12.3) |
| **Overall Outcome** | | | |
| Alive | 277 (63.6) | 192 (72.7) | 85 (49.7) |
| Abandonment | 73 (16.8) | 30 (11.4) | 43 (25.1) |
| Dead | 85 (19.5) | 42 (15.9) | 43 (25.1) |
| **Present Status** | | | |
| Remission | 352 (80.9) | 218 (82.6) | 134 (78.4) |
| Relapse | 83 (19.1) | 46 (17.4) | 37 (21.6) |
| **Relapse as to Location** | | | |
| Bone Marrow | 51 (61.4) | 25 (54.3) | 26 (70.3) |
| CNS | 27 (32.5) | 17 (37.0) | 10 (27.3) |
| Testicular | 1 (1.2) | 1 (2.2) | - |
| Multiple sites | 4 (4.8) | 3 (6.5) | 1 (2.7) |
| Bone Marrow, testicular | 1 (25.0) | 1 (33.3) | - |
| Bone Marrow, CNS, Orbital | 1 (25.0) | 1 (33.3) | - |
| Bone Marrow, CNS | 1 (25.0) | 1 (33.3) | - |
| Bone Marrow, CNS, testicular | 1 (25.0) | - | 1 (100) |
| **Duration from Diagnosis to Relapse** | | | |
| Less than 18 months | 45 (54.2) | 21 (45.7) | 24 (64.9) |
| Bone Marrow | 27 (60.0) | 11 (52.3) | 17 (70.8) |
| CNS | 14 (31.1) | 8 (38.1) | 6 (25) |
| Multiple sites | 3 (6.7) | 2 (9.5) | 1 (4.1) |
| More than 18 months | 38 (45.8) | 25 (54.3) | 13 (54.1) |
| Bone Marrow | 25 (65.8) | 16 (64.0) | 9 (69.2) |
| CNS | 11 (28.9) | 7 (28.0) | 4 (30.8) |
| Multiple sites | 1 (2.6) | 1 (4.0) | - |
| Testicular | 1 (2.6) | 1 (4.0) | - |
| **Duration from Relapse to Death (months)** | 8.2 ± 9.4 | 14.8 ± 15.7 | 8.3 ± 9.8 |
| **Status of the Relapse Group** | | | |

| Characteristic | All population (N = 435) | Standard Risk Group (N = 264) | High Risk Group (N = 171) |
|---|---|---|---|
| | Frequency (%); Median (range); Mean ± SD | Frequency (%); Median (range); Mean ± SD | Frequency (%); Median (range); Mean ± SD |
| Remission | | | |
| Dead | 6 (7.2) | 6 (13.0) | - |
| On Treatment | 53 (63.9) | 23 (50.0) | 30 (81.1) |
| Palliative | 23 (27.7) | 16 (34.8) | 7 (18.9) |
| | 1 (1.2) | 1 (2.2) | - |
| **Causes of Death** | | | |
| ARDS | 6 (7.1) | 3 (7.1) | 3 (7.0) |
| Septic Shock | 54 (63.5) | 28 (66.7) | 26 (60.5) |
| Respiratory Failure | 3 (3.5) | 1 (2.4) | 2 (4.7) |
| Dengue Shock | 1 (1.2) | 1 (2.4) | - |
| Intracranial Bleed | 10 (11.8) | 4 (9.5) | 6 (14.0) |
| Cardiogenic Shock | 1 (1.2) | - | 1 (2.3) |
| Multiple Organ Dysfunction | 4 (4.7) | 2 (4.8) | 2 (4.7) |
| Syndrome (MODS) | | | |
| Unknown | 6 (7.1) | 3 (7.1) | 3 (7.0) |

Based on the Kaplan-Meier survival analysis, the 5 year OS for acute lymphoblastic leukemia (figure 1) and EFS (figure 2) rates were 65.3% and 62.8%, respectively. The 5 year OS for standard risk ALL was 68.8% and for high risk patients was 50% (figure 3). The 5 year OS for the patients in remission was 83.7% while for those who had relapse was 21.1% (figure 4).

**Figure 1.** 5 year Overall Survival of children with ALL diagnosed between 2012 to 2016

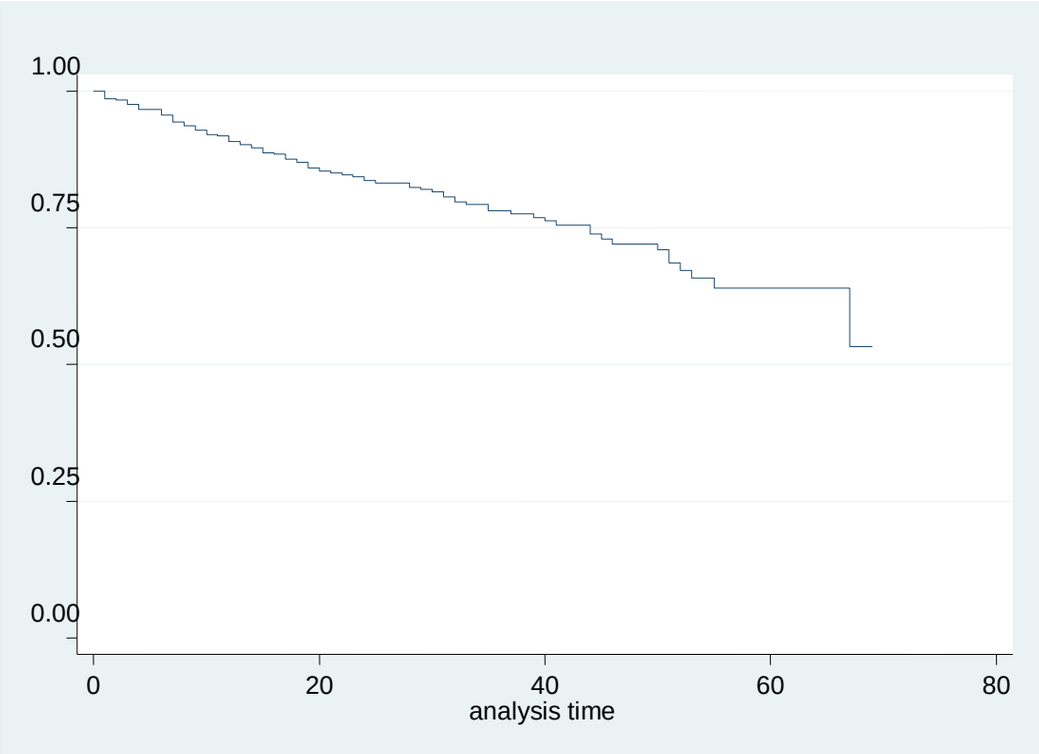


**Figure 2.** 5 year Event Free Survival of Children with ALL diagnosed between 2012 to 2016

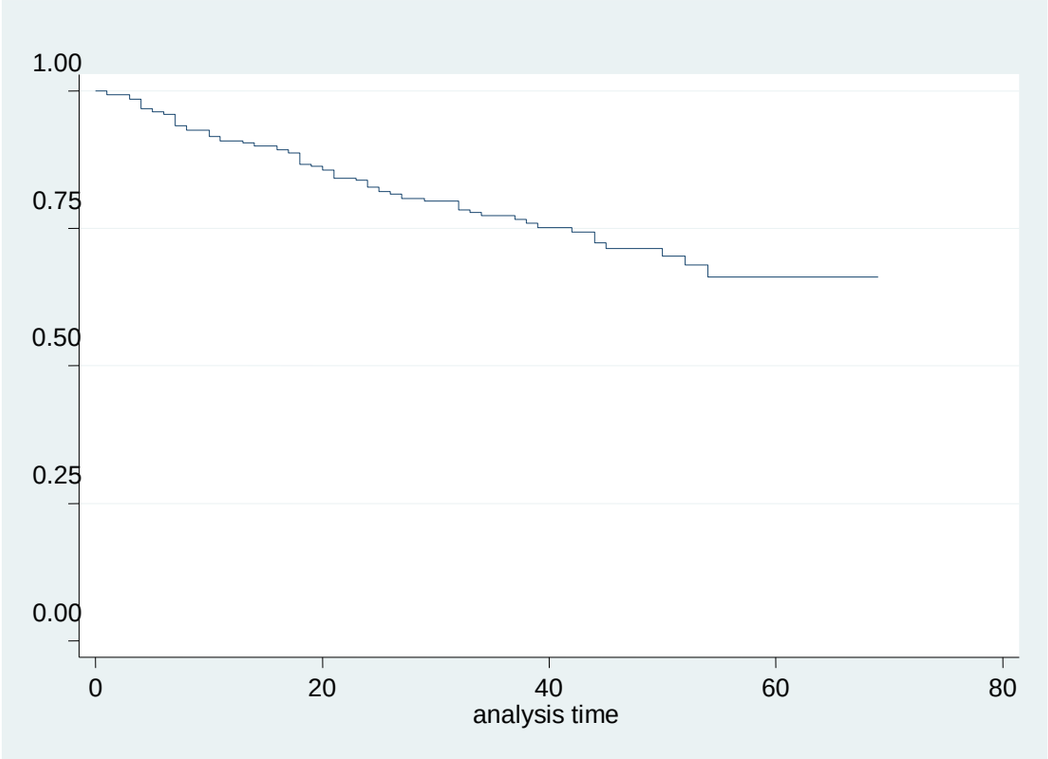



**Figure 3.** Overall Survival based on Risk Stratification of Children with ALL

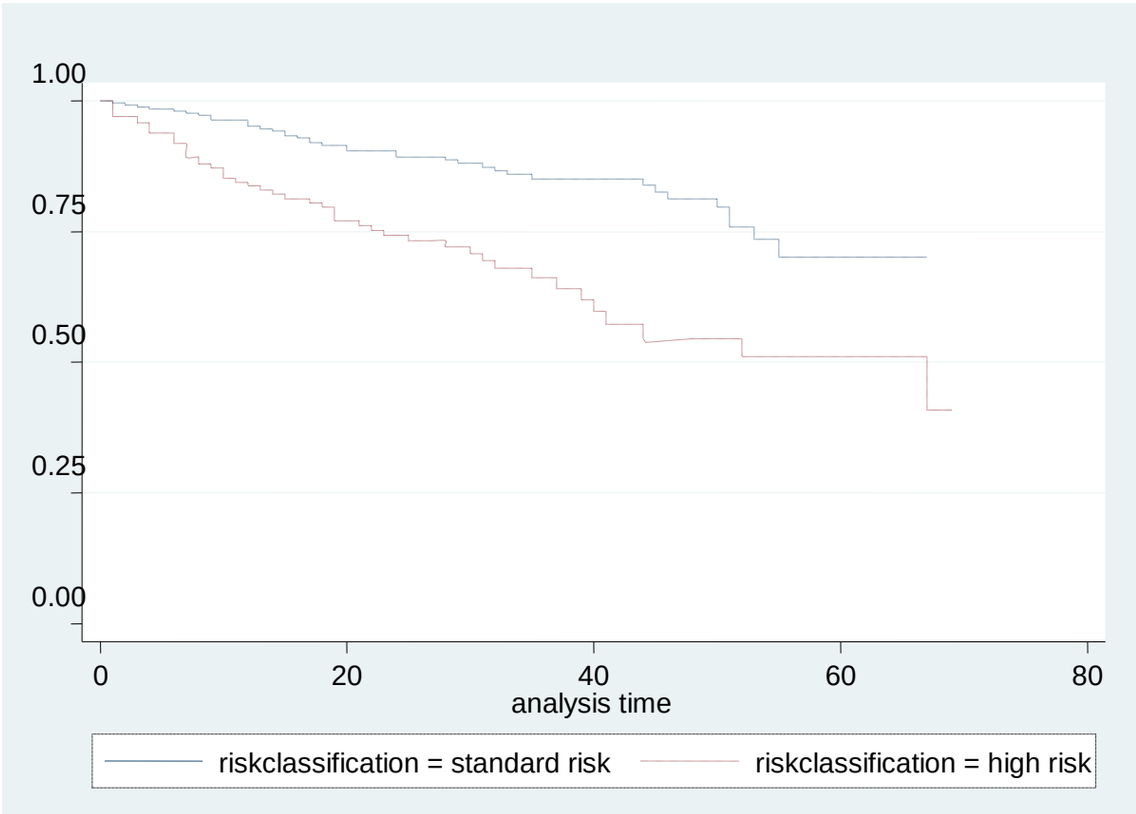
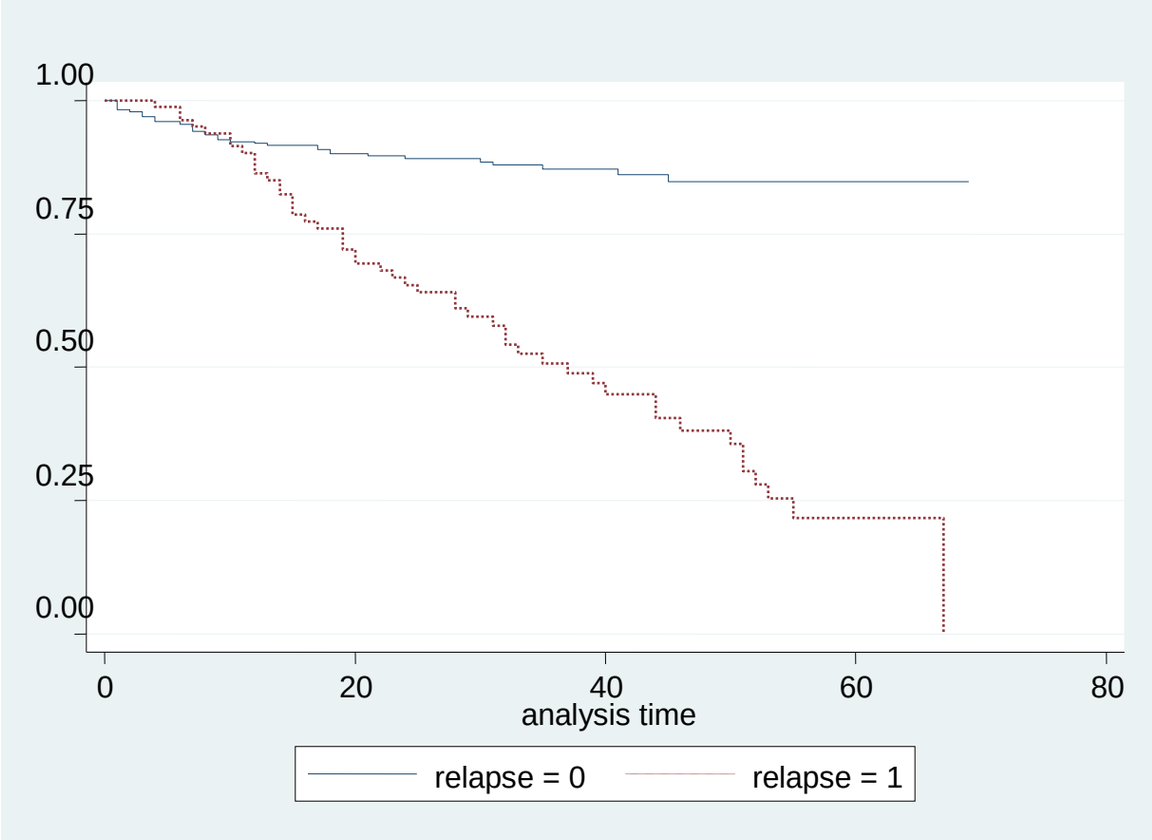


**Figure 4.** Overall Survival of children with ALL on Remission versus Relapse




Univariate and multivariate Cox proportional hazards regression in Table 3 revealed WBC count at diagnosis, risk classification, and immunophenotyping have a significant prognostic impact for development of relapse. Age and gender was reported with no prognostic significance.

**Table 2.** Factors Associated with Relapse

| Variable | Univariate | | Multivariate | |
|---|---|---|---|---|
| | Hazards Ratio | P-Value | Hazards Ratio | P-Value |
| **Age** | 0.85 | 0.486 | - | - |
| **Gender** | 1.25 | 0.245 | - | - |
| **Risk Classification** | 3.52 | 0.000 | 3.08 | 0.000 |
| **WBC count on Diagnosis** | 1.00 | 0.000 | 1.07 | 0.025 |
| **Immunophenotype** | 2.88 | 0.000 | 2.09 | 0.028 |

Univariate and multivariate Cox proportional hazards regression in Table 2 revealed WBC count at diagnosis, risk classification, immunophenotyping, and development of relapse have a significant prognostic impact for mortality. Age and gender was reported with no prognostic significance

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**Table 3.** Factors Associated with Rate of Mortality

| Variable | Univariate | | Multivariate | |
|---|---|---|---|---|
| | Hazards Ratio | P-Value | Hazards Ratio | P-Value |
| **Age** | 0.98 | 0.435 | 0.93 | 0.011 |
| **Gender** | 1.30 | 0.232 | - | - |
| **Risk Classification** | 2.62 | 0.000 | 2.98 | 0.000 |
| **WBC count on Diagnosis** | 1.00 | 0.000 | 1.00 | 0.034 |
| **Immunophenotype** | 2.51 | 0.001 | 1.91 | 0.037 |
| **Relapse** | 4.97 | 0.000 | 4.52 | 0.000 |

## DISCUSSION

Patterns of cancer care vary across countries of different income levels. Countries also have different capabilities for cancer care, depending on resource availability. Combined successes in cancer prevention, early detection, screening, and treatment have resulted in a reduction in overall cancer mortality rates in some more developed countries, predominantly as a result of declines in the incidence and/or mortality from a number of specific types of common cancer. [22]

The Philippines belonged to the LMIC for which a lot of barriers to screening, diagnosis, and treatment of childhood cancer have been a predicament. These barriers occur at all steps. Patients and parents may not be aware of signs and symptoms of childhood cancer, may rely on nonmedical forms of treatment, and may not have the transportation or money to travel to a primary care facility. If the patient arrives to the primary care, personnel may not be trained to recognize childhood cancer, laboratory and diagnostic imaging equipment may not be available to screen for cancer, and the patient or clinic may lack money to pay for necessary testing and treatment. Similar barriers make access to tertiary care and correct diagnosis problematic.[1] Hence, survival against childhood cancer during the past 2 decades was scarce.

In 2006, the Philippine Children's Medical Center created an innovative demonstration project to raise public awareness about the curability of childhood cancer as well as introduced to the community how to recognize the early signs of cancer to prevent delay in diagnosis, to catch them early and to treat them timely. Six years later, in 2012, the number of the newly diagnosed childhood ALL compared to the study of Galano has increased by 75% (111 newly diagnosed patients with ALL from 2003 to 2007 compared to 447 newly diagnosed cases from 2012 to 2016). The better public awareness of the first signs of cancer and the ability of health care professionals to diagnose the disease has efficiently changed the paradigm.

Earlier, inequities to treatment occurred in the Philippines as only those who can afford the treatment will survive and those that belonged to the lower income group did not receive treatment at all. Recognizing the need of the country to support the treatment of childhood ALL, the Department of Health in 2009 began sourcing chemotherapeutic drugs to some of the government hospitals so those who were less fortunate can have a chance for cure, this was the Acute Lymphoblastic Leukemia Medicine Access Program (ALL MAP). The Philippine Health Insurance Corporation (PhilHealth) in July 2012 launched the 'Z benefit' package for ALL with the aim to not just cover the hospital expenses but also ensure totality of care and attainment of better health outcomes. With these medical assistances from the government, the survival rate changed dramatically from 32.3% (from the DOH Rizal Cancer Registry) to 65.3% (OS reported in this study).

The improvement in the survival of childhood ALL is mainly due to the adoption of modifications in therapy based on individual pharmacodynamics and pharmacogenomics, risk-adapted therapy and improved supportive care.[23] One of the great achievements of pediatric oncology in recent decades is the refinement of risk stratification systems, allowing for an assessment of the aggressiveness of a particular child's cancer and for treatment intensity to be matched to disease risk, thereby reducing both under-treatment and overtreatment.[24] Stratification into risk groups is based on a range of clinical, biological and genetic features, such as age and gender, WBC count at diagnosis, immunophenotypic, cytogenetic and molecular characteristics, and early medullar response to induction therapy.[25]

Although age of less than 1 year old and more than 10 years old as well as the male gender were considered in the NCI/Rome Criteria as high risk, results in this study showed no significant prognostic impact, this was in parallel with the Lituania study.[26] Likewise, in an eight year study done in 160 patients in Bulgaria, sex and age were found to be not significant prognostic factor for the development of relapse and death.[27] A study done in El Salvador also showed comparable results.[28] Similar results were also noted in a study done by Dujua and Galano.[7,12] Hossain analyzed 14192 children in the Surveillance Epidemiology and End Results (SEER) data during 1973–2009 which showed significant variability in pediatric ALL survival by age at diagnosis. In a multivariable Cox proportional hazard model stratified by year of diagnosis, those diagnosed in age groups 1–4, 5–9, 10–14, and 15–19 years were 82%, 75%, 57%, and 32% less likely to die compared to children diagnosed in infancy, respectively. Male gender showed hazards ration of 1.29 at p-value of <0.0001.[29]

In this study, out of 435 subjects, 95 (21.5%) showed WBC count of more than 50,000/mm$^3$, out of this 95 subjects 37 (38.9%) showed high risk immunophenotype. Twenty seven subjects (28.4%) were more than 10 years of age. From among the subjects with elevated WBC count of more than 50,000/mm$^3$, outcome showed 46 (48.4%) alive out of 95, the 18 (18.9%) abandonment and 31 (32.6%) dead. Cox regression analysis showed significant hazards ratio with WBC count on diagnosis which is compatible with the reports of other studies. Hazard analysis done in Lithuania revealed WBC at diagnosis to have a significant prognostic impact for an event.[26] The results were compatible with the study in Bulgaria for developing relapse and death.[27] In a study among Filipino children by Dujua, WBC count was insignificant to lead to relapse which was in parallel with the results in a study by Galano.[7,12]

According to risk classification by the NCI/Rome Criteria, high risk patients have significantly lower survival compared to the standard risk patients. Cox regression analysis in this study showed significant risk for mortality rate. This was compatible with the results seen in the Bulgarian study with events leading to relapse and death.[27] Similar results were seen in the study by Dujua with p-value of <0.001 risk for relapse.[12]

Significant prognostic factor that lead to mortality was seen in patients with immunophenotype T-cell ALL, biphenotypic ALL, and mature B cell ALL. Similar results were seen in the study by Hossain for T-cell ALL.[30] While in the study of Dujua, p-value was not significant at 0.740.

In this study 19.1% of the subjects developed relapse. Among the relapsed patients, 31.0% were reported with WBC more than 50,000/mm$^3$, 11.5% were of high risk immunophenotype, and age of more than 10 years old were seen in 19.5%. In a study by Galano relapse showed significant hazard for rate of mortality.[7] Very early relapses are those that occur within 18 months of initial diagnosis. The clinical behavior of early relapse is aggressive with less than a third survived. However, about 50% of patients with late relapse will survive. An isolated bone-marrow relapse indicates a worse prognosis than combined marrow and extramedullary relapse which, in turn, is worse than isolated extramedullary relapse.[30] Out of the 83 patients who relapsed, there were 54.2% who developed relapse in less than 18 months, 79.1% of from this early relapsers died within 455.5 $\pm$ 532.5 days, while for the group who relapsed more than 18 months 45.8% comprised this group, 51.4% among the late relapsers died within 1266 $\pm$ 546.6 days in this study.

Survival rates of childhood ALL in this study were inferior compared to those reported in the Western countries. The 5 year OS in this study was however similar to other LMIC such as Thailand showing OS of 67.2% in study by Seksarn among 486 children from 12 institutions.[31] The study in Brazil done last 2000-2005 showed an OS of 62.4%[32], Brazil belonged to the upper middle income countries. However, this was not comparable to the results in the study of Dujua among Filipino children with the 5 year OS of 86.94%. The difference with the treatment protocol in the Modified BFM95/HKALL97 with the study of Dujua was that they utilized methotrexate of 2g/m$^2$ for their standard risk ALL during the consolidation phase. Being a part of the LMIC group, we modified the methotrexate dose at 1g/m$^2$ in consolidation phase for our standard risk ALL, as most of our patients cannot afford the high cost of the drug as well as the methotrexate assay levels. In the BFM95 ALL study, they utilized methotrexate dose of 5g/m$^2$, which was modified with the HK ALL97 study using 2g/m$^2$, results of the HK ALL97 in 171 patients showed 4 year OS of 86.5%. According to Pui, the best dose of methotrexate depends on the leukemic cell genotype and phenotype and host pharmacogenetic and pharmacokinetic

variables. Methotrexate at 1–2 g/m$^2$ is adequate for most patients with standard risk ALL. The fairly low accumulation of methotrexate polyglutamates in blast cells with either *TEL-AML1* or *E2A-PBX1* fusion suggests that patients with these genotypes could also benefit from an increased dose of methotrexate. However, mega doses of methotrexate do not seem necessary for patients with ALL.[24]

One of the possible reasons for the lower survival of our patients compared to international trials could be due to presence genetic aberrations that are high risk for treatment failure or relapse. The advent of fluorescent in situ hybridization and molecular diagnostic techniques allow the detection of these cytogenetic abnormalities. However, these are not routinely done in our setting due to its high cost. Adverse genetic abnormalities include *MLL* rearrangements and hypodiploidy < 44 chromosomes.[24] A number of structural abnormalities that convey worse prognosis include chromosome band 11q23; translocations involving proto-oncogenes on chromosome 8, 9, and 22; translocation of the MYC proto-oncogene from chromosome 8 to an immunoglobulin gene, either the heavy chain on chromosome 14 or the light chains on chromosome 2 and 22, respectively; the Philadelphia (Ph) chromosome, with its t(9:22)(q34;q11) translocation; and translocation t(1:19)(q23;p13) found in cytoplasmic immunoglobulin M-positive pre-B-cell ALL.[33] Furthermore, several of the alterations that most often emerge at relapse are also associated with poor treatment outcomes when present at diagnosis—eg, deletions of *IKZF1*, *CDKN2A*/*CDKN2B*.[34]

Another possible cause for the decrease survival is the delay in the treatment. The cause is either due to the patient or family's decision to suspend treatment without medical advice or due to hematologist's decision to suspend treatment. In our institution, the main reasons of the patient and their family for the delays in the treatment and non-adherence to the protocol schedule is due to financial constraints from lack of funds for travel, medications and food allowance, no adult travel companion available to escort the child to the hospital for their treatment, and unavailability of transportation for the patients living in far flung areas of the country. Undue interruptions from the side of the hematologist are due to presence of moderate to severe infections, low absolute neutrophil counts, low platelet count of less than 50 x $10^9$/L, and elevated liver transaminases during maintenance phase. A study done in Brazil regarding compliance with the treatment protocol mentioned that the reason for interruption included decreased leukocyte and/or neutrophil count, elevated aminotransferases, upper respiratory tract infections, bronchitis and other reasons not specified.[35] They found out that the reasons for undue interruption of chemotherapy by physicians included aminotransferase below levels pre-established by the protocol for adjusting the chemotherapy doses, and leukopenia and neutropenia, with values above the cutoff levels in the protocol. They found out that the longer the "appropriate" suspension of chemotherapy, the lower the likelihood of relapse. For graphical display, the investigator dichotomized the variable into two strata: children with less than or more than 2% of "appropriate" chemotherapy interruption. This interruption equals a two-week break for children who completed the whole of the maintenance phase. The probability of EFS for the group with less than 2% of interruption was 33.3 ± 13.6%. For the group with more than 2% of interruption, the EFS was 80.3% ± 5.1%.[35] Strict adherence to treatment protocols and rigorous monitoring of both the doctors and patients will contribute to better treatment results.

The occurrence of treatment abandonment, as often observed in LIC/LMIC, is of major concern because it prevents the correct administration of the full treatment regimen to the child with cancer and affects the effectiveness of the treatment and prevents observing the patient's final state. Many reasons for abandonment have been cited, including a lack of financial resources, poor disease comprehension, cultural factors, belief in alternative medicines, fear of treatment toxicity, inadequate care on the part of health care workers, and decreased awareness of aid programs.[36] Abandonment in our center was noted to be high in 2012 at 44.4%, then in 2013 it decreased to 15.1%, in 2014 abandonment rate was noted at 10.7%, in 2015 at 10.5% and in 2016 at 9.9%. In 2013, the patient navigation program for the ALL MAP was launched in the country with the aim to track and monitor patients, direct patients to resources, and provide compassion and empathy to help them understand their disease. Abandonment rate has declined since 2013 owing to the navigation program. Hence, further improvement on patient tracking, counseling and education among cancer centers should be strengthened to improve patient compliance.

Febrile neutropenia is one of the most serious hematologic toxicity seen in cancer

patients receiving chemotherapy. Delay in treatment due to infections contributes to low survival. Timely and effective supportive care is critical for the successful treatment of ALL. Indeed, the intensity of treatment for ALL must be appropriate for the level of supportive care that is available.[37] Indiscriminate adoption of high-intensity treatments from developed countries is inappropriate, without a commensurate level of supportive care. Over-treatment beyond the limits of supportive-care capabilities can lead to excessive induction death and high abandonment rates.[38] In this study, induction death was 1.4% (6 out of 435) of which 50% is due to septic shock followed by 16.7% due to respiratory failure, 16.7 % due to intracranial bleed and 16.7% due to cardiogenic shock. Currently in countries with basic, and even limited resources, the induction death rate is approximately 30%, exceeding even the total cumulative risk of relapse.[39] Deaths from infection and bleeding are most common. In one study from Northern India, sepsis and bleeding accounted for 53.3% and 15.7% of deaths, with tumour lysis syndrome contributing to 6.3% of deaths.[40] Prevention of infection by simple means is a cost-effective strategy. Patients on chemotherapy should preferably be admitted to a separate ward away from those with infectious diseases. Hand hygiene is especially important to prevent cross infection. Hand-washing facilities with easy accessibility should be made available in the wards, or disinfectant hand gels can be placed at the bedside.[37] These measures are being followed in our institution. We also have an infectious control committee in the center that evaluates and monitor infection control practice and reviews the febrile neutropenia protocol based on the local bacterial sensitivity in the ward. Monthly meeting of the Infection Control Committee recognized the aspects and areas of improvement to maintain good infection control program.

The strength of the CCG 1961 protocol making it suitable for the high risk patients was the double delayed intensification phases. The reported outcomes from 1996 to 2002 for the CCG 1961 trial by Bhojani showed EFS of 71.3% $\pm$ 1.6%.[13] A study done by Nachman in ALL patients aged 16-21 using the same protocol, reported 5 year EFS of 68%.[41] In a study by Bleyer among adolescents and young adults using the CCG 1961 protocol, OS showed 77.5%.[42] The study of Galano showed 77.8% EFS for the high risk group. This study showed OS of 50% which has lower survival compared to the result of the trials mentioned. Factors that contributed to the lower survival include treatment interruption, lack of cytogenetics study to identify genetic aberrations that could contribute to being high risk for relapse and treatment failure, as well as abandonment. Abandonment rate identified in this study for high risk group was higher at 25.1% compared to standard risk ALL at 11.4%.

The 5 year OS for the patients on remission was 83.7% and for those who developed relapse was 21.1% which is comparable with the study done in Central America showing OS of 28.3% $\pm$ 1.9%. The median follow up time for the patients who did not experience another event was 1.9 years.[43] While in our institution, the median follow up time from diagnosis to death among the relapsed group showed 2.4 $\pm$ 1.5 years (relapsed in less than 18 months 1.2 $\pm$ 1.5 years and the group who developed relapse in more than 18 months 2.4 $\pm$ 1.5 years). In the multivariate analysis done in the Central America by Chan time to relapse of less than 36 months, CNS status at diagnosis, age and WBC count at diagnosis showed significant prognostic EFS.[33] This results were similar to the study done by Marjerrison in Central America showing in multivariable analysis, worse post-relapse survival was associated with age > 10 years, white blood cell count > 50 X $10^9$/L, and positive central nervous system status at the original ALL diagnosis, relapse that was not isolated central nervous system or testicular, and relapse < 36 months following diagnosis.[39] Prognosis after relapsed is poor but a substantial number of those who relapsed more than 18 months from the time of diagnosis showed prolonged survival compared to the early relapsers.

## CONCLUSION

Cure rates for childhood ALL has improved remarkably over the past 50 years, as many treatment protocols have been developed and succeedingly modified with the goal of multimodal principle of synergistic effect with the least toxicities. The present study summarized the survival rate of childhood ALL in a single state tertiary treatment center for childhood cancer.

The 5-year overall and event-free survival rates were lower than those reported for developed countries but is comparable with reports of other LMICs. This outcome will serve as a framework for future improvements. Prognostic factors for relapse and mortality such as WBC count at diagnosis, risk classification, and immunophenotyping are comparable with other studies. Relapse has a significant prognostic impact for mortality. Development of accessibility to care, increase

awareness, early detection and resources at hand should be achieved. Improvement in the follow up protocol to prevent delays in the treatment, patient education to prevent non-compliance and psychosocial support, to developed better supportive care, and expand facilities should be given emphasis to further improve survival and prevent relapse.

Outcome for relapsed ALL remains poor hence, better chemotherapy regimen for improving survival should be studied. Various protocols for relapse have been studied but reported OS range from 25-30% with increase toxicities reported in these trials. Infection is a frequent and serious problem in cancer patients on chemotherapy. Effective supportive care is critical to successful treatment. Prevention of infection by simple means such as good hand hygiene should be emphasized to prevent delay in treatment due to infection. Employment of cytogenetic testing as part of diagnostic risk classification should be perform to recognize the group that are high risk so more intensified treatment protocol will be offered to increase survival. Overall, the adopted treatment protocols for childhood ALL in this institution showed acceptable results as survival has remarkably improved compared to the report in 2010 taken from the population based registry in DOH Rizal Cancer Registry at 32.3% to the present 65.3% OS in this study.

Future studies to evaluate the different relapsed protocol (MSK-NY-II for bone marrow and multiple site relapse and POG 9431 for isolated CNS relapse) adopted in the center should be done to facilitate better understanding of outcomes for relapse. Options such as hematopoetic stem cell transplant and immunotherapy should also be studied.

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