



SURVIVAL OF CHILDREN WITH ACUTE LEUKAEMIA: A SINGLE CENTRE EXPERIENCE

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Abstract

Introduction: Acute leukaemia in children accounts for 25-30% of malignant diagnosis. Survival from acute leukaemia continue to improve. Treatment outcome depends on factors like gender, age at diagnosis, parental education, the initial total white cell count (TWC), cerebrospinal fluids (CSF) infiltration, immunophenotype and treatment response. **Objectives:** The objectives were to evaluate the survival of children with acute leukaemia who received chemotherapy and identify relevant factors. **Methodology:** The study was a retrospective record review at the Paediatric Oncology Unit, Hospital Universiti Sains Malaysia (Hospital USM). The data collected depending on pre-set research proforma from the year 1990 to 2010. Survival analysis of each type of leukaemia was completed using multiple Cox regression model. **Results:** A total of 334 cases were identified, only 283 patients received treatment at Hospital USM. There were 224 patients with acute lymphoblastic leukaemia (ALL) and 59 with acute myeloid leukaemia (AML). Overall survival (OS) rate at 3 months for ALL and AML were 89.3% and 72.9% respectively. The event-free survival (EFS) rate for ALL at 1, 3, and 5 years were 69.6%, 54.1% and 47.8% respectively. For AML, the EFS rate at 1, 3, and 5 years were 52.0%, 42.4% and 38.1% respectively. Multiple Cox regression model showed children's age at diagnosis and early response to steroid therapy were the most significant prognostic factors for ALL survival, whereas the spleen size and treatment protocol were the most significant prognostic factors for AML. **Conclusion:** Survival rate in this study was comparable to developing countries. ALL had better outcome compared to AML.

Keywords:

Survival Analysis, Acute Leukaemia, Acute Lymphoblastic Leukaemia, Acute Myeloid Leukaemia

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Introduction

Acute lymphoblastic leukaemia representing approximately 80% of childhood leukaemia. The worldwide incidence has gradually increased annually. Untreated diseases are associated with early childhood mortality. The survival rate has improved significantly with the modern treatment modalities [1,2]. The survival rate of children with acute lymphoblastic leukaemia (ALL) is better than acute myeloid leukaemia (AML) with overall survival (OS) at 83% (95% CI: 80-85) for ALL, and 54% (95% CI: 46-62) for AML in Northern Europe (3). A recent study stated that ALL survival rate has been improved significantly with 5-year-survival rate of 83.7% in 1990-1994 to 90.4% in 2000-2005 [4]. In Malaysia, the 2-year-survival rate for ALL from 1980-1995 was 67% [5].

A 5-year-survival rate for ALL was the highest in age group 1-4 years old with 87% and at 60% for AML in the similar age group. Advancement in chemotherapy has been shown to favourably increase the curative rate in ALL. More than 95% achieved complete remission (CR) with 5-year disease free survival rates at 63-83% [6]. The risk of relapse mostly depends on previously identifiable risk factors. Standard risk (SR) factors are age between 1-10 years old, initial TWC < 50 x 10⁹/L, absence of central nervous system and testicular involvement, T cell immunophenotype, M3 marrow on Day 15 or M2/M3 marrow on Day 36 and DNA index 1.16-1.6 (2). Risk stratification

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has been modified into 4 groups as per Children's Oncology Group (COG) findings [7]. Younger age group and low TWC at diagnosis usually have better prognosis in AML patients. Children with Down Syndromes especially if the age less than 4 years old at the time of diagnosis tends to have a better outcome. The gender factor showed that females had a better survival rate than males [2,8].

The objective of the study is to determine the survival of children with acute leukaemia (ALL and AML) who received chemotherapy in Paediatric Oncology Unit at Hospital USM from the 1st January 1990 - 31st December 2010.

Methods

The study was conducted in Paediatric Oncology Unit at Hospital Universiti Sains Malaysia (Hospital USM), Kubang Kerian, Kelantan. Hospital USM is the pioneer for paediatric oncology in the East Coast of Peninsular Malaysia. Most of the patients originated from 3 neighbouring states (Kelantan, Terengganu and Pahang). These patients undergone chemotherapy and follow up treatment at Hospital USM. Patient records were retrieved retrospectively from ward registry for the diagnosis of ALL and AML. Confirmatory cases were from microscopic and cytological findings. Enrolled patients were those who started treatment from 1st January 1990 until 31st

December 2010. Case notes were reviewed and information was obtained according to the proforma. Ethical approval was granted by the Universiti Sains Malaysia Ethical Committee (USMKK/PPP/JEPeM [238.4.(1.10)]) prior to the commencement of the study. Inclusion criteria were children with confirmed ALL or AML, receiving treatment at Hospital USM and age from newborn to 14 years old at the time of diagnosis. Exclusion criteria were cases with incomplete information such as treatment outcome, and patients who were transferred out to other hospital for continuation of chemotherapy.

Kaplan-Meier survival curves were used to calculate OS, event free survival (EFS) and log rank test were used to compare the survival curves of the subgroups. The factors investigated were age at the time of diagnosis, gender, immunophenotype, type of leukaemia, size of spleen and liver, early treatment response and CSF involvement. The proportion of events (resistance, relapse, death, complication) were compared using chi-square test. Univariate and Multivariate cox proportional hazard model were used to explore predictors of OS and EFS. The *p* value of < 0.05 is considered as significant. For the purpose of the study, definition below (Table 1) was used to calculate the parameters listed above.

Table 1: Table of definition

Definitions	
1.	Duration of survival is taken from the date of diagnosis
2.	Overall survival is taken from the time diagnosis to death or last contact
3.	Event free survival is time from diagnosis to the date of any event or to the date when patient was confirmed to be well, at the date of censor which ever occurred first
4.	Event is considered as resistance disease, relapse, defaultment, death or major complications (major complication is defined as presence of any recorded complications or secondary cancers)
5.	Median survival is the time when half of patients are expected to be alive (the chance of surviving beyond that time is 50%)
6.	Disease free survival is measured from time of completed treatment until remission or no disease
7.	Initial total white cell is the documented TWC at presentation, before starting treatment
8.	Complete remission is presence of less than 5% blast cells in bone marrow in the absence of leukemic blast cells in the peripheral blood and cerebrospinal fluid, normal peripheral blood count and absence of localized disease
9.	Relapse is any disease recurs in bone marrow, central nervous system or testis
10.	Bone marrow relapse is presence of 25% blast cells in bone marrow
11.	Central nervous system (CNS) relapse is presence of any CNS manifestation without any other explanation with or without presence of blast in cerebrospinal fluid
12.	Testicular relapse is presence of testicular mass on examination or ultrasound
13.	Good early response is absence of blast in peripheral blood on day 8 of treatment with steroid
14.	Poor early response is presence of blast cells in peripheral blood on day 8 of treatment with steroid
15.	Undetermined early response is uncertainty of blast cells in peripheral blood on day 8 of treatment with steroid

Result

A total number of 334 acute leukaemia patients (ALL and AML) were identified during the study period (1st January 1990 to 31st December 2010). Out of that, 257 (77%) patients were ALL and 77 (23%) were AML. For ALL patients, 224 patients fulfilled the inclusion criteria and 33 were excluded. For AML patients, 59 were enrolled and 18 were excluded. There were 11 patients (19%) identified as Down syndrome in this study. There were 60.1% of males and 39.9% of females in this study. The incidence of acute leukaemia was 1.5 times higher in males as compared to females. Majority of the patients were Malay ethnicity (97.4%). About 21.2% of their parents had tertiary educational background and 23% had poor educational background (Table 2).

The common age group for ALL patients was 1.1-4.9 years (55.8%) with mean age of 4.9 years old. Majority of them presented with TWC of less than 100.0 x 10⁹/L (75.8%). Mean TWC at the time of

presentation was 77.0 x 10⁹/L. There were 71.4% from B cell subtype, 20.5% from T cell and 3.6% from mixed lineage. Good early response to oral steroid was seen in 46.4% and 43.3% had poor early response. Most of the patients were stratified into the high risk treatment group, with 56.3% using EORTC-VHR protocol, 1.8% using UKALL 97 (Regime B/C) and 2.2% using Infantile Regime. About two third of ALL children completed chemotherapy (67%). More than half of ALL patients (59.8%) were alive at the end of the study period. For AML patients, 62.7% presented in the age group from 2.1 to 10 years old. The mean age at diagnosis was 6.4 years old. For the AML treatment, 59.3% of the patients received AML BFM 87 and 40.7% were on AML 12 UK Protocol. There were equal proportions of patients who completed chemotherapy, and who did not, which were 49.2% and 50.8% respectively. At the end of the study period, 40.7% were still alive (Table 3).

Table 2: Demographics profile of children with acute leukaemia registered in HUSM from 1990 - 2010

Features	All Patients (n=283) no (%)	ALL (n=224) no (%)	AML (n=59) no (%)
Gender			
Male	170(60.1%)	137(61.2%)	33 (55.9%)
Female	113(39.9%)	87 (38.8%)	26 (44.1%)
Race			
Malay	276(97.4%)	218(97.3%)	58(98.3%)
Chinese	3(1.1%)	3(1.3%)	0
Indian	1(0.5%)	0	1 (1.7%)
Others	3(1.1%)	3(1.3%)	0
Parental Education			
Primary	49 (17.3%)	41(18.3%)	8 (13.6%)
Secondary	109(38.5%)	90(40.2%)	19(32.2%)
Tertiary	60 (21.2%)	43(19.2%)	17 (28.8%)
Missing data	65 (23%)	50(22.3%)	15 (25.4%)

Table 3: Clinical profiles of children with ALL and AML

Features	ALL n (%)	AML n (%)
Age at diagnosis		
≤ 1 year	7 (3.1)	8 (13.6)*
>1 - 4.9 years	125 (55.8)	
5 - 9.9 years	72 (32.1)	37 (62.7)**
≥ 10 years	20 (8.9)	14 (23.7)
TWC at Diagnosis		
≤ 100 x 10 ³ /μL	170 (75.8)	50 (84.7)
> 100.1 x 10 ³ /μL	48 (21.4)	8 (13.6)
Missing data	6 (2.7)	1 (1.7)
ALL Subtypes		
B cell	160 (71.4)	
T cell	46 (20.5)	
Mixed	8 (3.6)	
Missing data	10 (4.5)	
AML Subtypes		
M 0		0 (0)
M 1		1 (1.7)
M 2		14 (23.7)
M 3		9 (15.3)
M 4		11 (18.6)
M 5		3 (5.1)
M 6		10 (16.9)
M 7		11 (18.6)
CSF involvement at Diagnosis		
Yes	9 (4)	0 (0)
No	213 (95.1)	59 (100)
Missing data	2 (0.9)	0
Liver size		
≤ 5 cm	157 (70)	51 (86.4)
>5 cm	63 (28.1)	9 (13.6)
Missing data	4 (1.9)	0
Spleen size		
≤ 5 cm	172 (76.7)	54 (91.5)
>5 cm	48 (21.4)	5 (8.5)
Missing data	4 (1.9)	0
Treatment Protocol		
EORTC_SR	78 (34.8)	
EORTC_VHR	126 (56.3)	
UKALL 97 Regime A	11 (4.9)	
UKALL 97 Regime B/C	4 (1.8)	
Infantile Regime	5 (2.2)	
AML BFM 87	-	35 (59.3)
AML 12 UK Protocol	-	24 (40.7)
Final Outcome		
Alive	134 (59.8)	24 (40.7)
Died	90 (40.2)	35 (59.3)

*Age group less than 2 years

** Age group between 2- 10 years

Overall Survival Analysis

In general, 55.8% of acute leukaemia patients were alive at the end of the study period. Immediate OS rate at 3 months after diagnosis was 85.9%. The OS rate were 74.9% at 1 year, 61.7% at 3 years, 58.5% at 5 years, and 53.1% at 10 years. Overall mean survival time was 163.7 (147.5 - 180.0) months.

For ALL patients, 58.9% were alive at the end of the study period. Immediate OS rate at 3 months after diagnosis was 89.3%. OS rate for ALL was 77.7% at 1 year, 66.9% at 3 years, 63.5% at 5 years, and 57.3% at 10 years after diagnosis. Overall mean survival time was 176.3 (158.5 - 194.1) months. For AML, 40.7% of patients were alive at the end of the study period. Immediate OS rate at 3 months was 72.9% after diagnosis. OS rate for AML was 59.3% at 1 year, and 41.4% at 3, 5 and 10 years respectively Overall median survival time was 20 (1.4 - 38.5) months. In our study, ALL had better OS rate compared to AML, which was statistically significant (p -value < 0.001).

In general, about 41.3% (n= 117) of patients who were diagnosed with acute leukaemia did not experience any events at the end of study period. The above figure showed overall median survival time was 40 (13.0- 67.0) months. Overall EFS rate was 66.0% at 1 year after diagnosis, 51.2% at 3 years, 45.6% at 5 years and 38.7% at 10 years. For ALL alone, 42.4% (n= 95) patients had no event at the end of study period. The median survival time for ALL was 48 (19.5- 76.4) months. EFS rate for ALL was 69.6% at 1 year after diagnosis, 54.1% at 3 years, 47.8% at 5 years and 39.8% at 10 years. For AML, about 37.3% (n=22) patients had no event at the end of study period. The median survival time for AML was 16 (5.6- 26.0) months. EFS rate for AML was 52.5% at 1 year after diagnosis, 42.4% at 3 years, 38.1% at 5 years and 30.5% at 10 years. EFS rate was better in ALL as compared to AML, with p value 0.039. Figure 1 showed the OS and EFS for children with ALL and AML using Kaplan- Meier model.

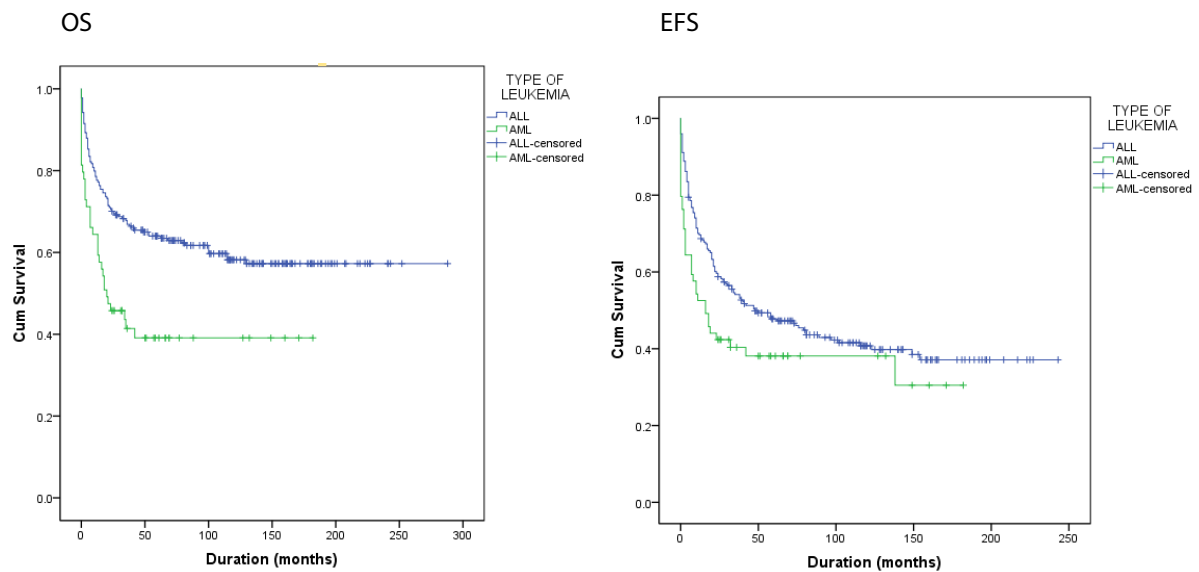


Figure 1: Kaplan- Meier estimates of OS and EFS for children with ALL and AML in Hospital USM

Males had better survival outcome as compared to females (42.4% vs 30.8%). Median survival time was 16 months (95% CI: 0.00-53.12) for males and 16 months (95% CI: 1.00 - 30.99) for females. EFS rate at 10 years after diagnosis for females were 33.0%, and 24.7% after 15 and 20 years respectively. Whereas for males, the EFS rates at 10, 15 and 20 years were similar at 42.0% after the diagnosis.

Relapse was one of the main concern for both ALL and AML patients. The most common site of relapse was isolated bone marrow (BM) findings in both cases. BM relapse occurred in 52 children with ALL and 14 children with AML. There were 7 cases with CNS relapse, 1 for testicular relapse and 3 for both bone marrow and testicular relapse in ALL patients. For bone marrow and CNS relapse, 7 ALL cases and 1 AML case were identified.

Simple Cox regression analysis that showed poor prognostic factors for ALL in this study were age group, aged 10 years old and above, high TWC at the time of diagnosis (more than $100.0 \times 10^9/L$), CSF involvement at diagnosis, poor or undetermined early response to oral steroid and those in high risk group. Hazard ratio was high in children more than 10 years (HR 3.07; 95% CI: 1.74 - 5.44). For other prognostic factors, the hazard ratio was high; in children aged 0.1 to 1.0 year (HR 2.99; 95% CI: 1.19 - 7.45); aged 5.0 to 9.9 years old (HR 1.52, 95% CI: 1.04 - 2.23); TWC more than $100.0 \times 10^9/L$ (HR 1.669; 95% CI: 1.11- 2.49); CSF involvement at diagnosis (HR 2.368; 95% CI: 1.15 - 4.85); poor early response to steroid (HR 1.546; 95% CI: 1.06 - 2.24); undetermined early response to oral steroid (HR 2.548; 95% CI: 1.32 - 4.98); and high risk treatment group (HR 1.564; 95% CI: 1.08 - 2.25).

In multiple Cox proportional hazard model, it showed children's age at diagnosis and early response to steroid therapy were the significant prognostic factors for our ALL survival. There was increased risk of death or relapse ALL in children aged ≥ 10 years old (95% CI: 1.70 - 5.54; $p < 0.001$), followed by children aged ≤ 1 year old (95% CI: 1.16 - 7.35; $p = 0.020$) and undetermined early response (95% CI: 1.18 - 4.44; $p = 0.014$). For AML, multiple Cox proportional hazard model (backward LR) showed spleen size and treatment protocol were the most significant prognostic factors for our AML survival. There was an increased risk of death or relapse AML in children with spleen size > 5 cm below subcostal margin (95% CI: 1.47 - 11.48; $p = 0.007$), followed by children who treated with AML BFM 87 protocol (95% CI: 1.33 - 6.26; $p = 0.007$) (Table 4).

Table 4: Prognostic factors for poor outcome in children with ALL and AML

Variable	Crude Hazard ratio (95% CI)	Wald statistic (df)	p-value
ALL			
Age			
>1.0-4.9 years	1.0		
≤ 1 years	2.29(1.16,7.35)	5.21(3)	0.022
5.0-9.9 years	1.51(1.02,2.25)	4.26(3)	0.039
≥ 10 years	3.07(1.70,5.54)	13.99(3)	<0.001
Early Response			
Good	1.0		
Poor	1.34(0.91,1.97)	2.25(2)	0.133
Undetermined	2.29(1.18,4.44)	6.04(2)	0.014
AML			
Spleen			
≤ 5 cm	1.0		
> 5 cm	4.01(1.44,11.12)	7.08(1)	0.008
Treatment Group			
AML 12 UK	1.0		
AML BFM 87	2.89(1.33,6.26)	7.30(1)	0.007

AML 12 UK and AML BFM 87 refer to treatment strategy used for acute myeloid leukaemia (AML)

Discussion

Majority of our patients (95%) originated from the East part of Peninsular Malaysia. Relapse in ALL occurred within 2 to 3 years after diagnosis, but for AML, it was within a year after diagnosis. The number of patients with acute leukaemia has

significantly increased from the year 1990 to 2010. The increment has gone up to more than 50% in the year 1990 - 1994 to the year 1995 - 1999, followed by 20 - 25% increment in the year 2005 - 2010. For AML, the rate of increment from 1990 - 1994 and 1995 - 1999 was about 25% and further increased up to 50% in year 2000 - 2004

and 2005 - 2010. The Hospital USM Oncology Unit has been set up in 1990 to accept referrals from neighbouring states which led to increase in number of cases. Many parents delayed seeking treatment, especially in 1990 - 1994 and seeking for an alternative therapy after clinical and laboratory diagnosis [9]. In literature, the incidence of acute leukaemia has increased due to various environmental factors such as chemical, benzene and air pollutants [10].

The demographic variables for ALL and AML, such as gender and age distribution in our study, were almost similar to other reported studies [1,3]. The incidence in male was 1.5 times higher than female [11]. Kelantanese were homogenously inhabited by Malay and Siamese and reflected in our demographic capture that the predominant race group was Malay (97.4%), followed by Siamese (1.1%), Chinese (1.1%) and Indian (0.5%). For the ALL subtype, B-cell subtype was the commonest followed by T-cell and mixed (biphenotype). These findings were almost similar as reported previously [12,13,14]. For AML, FAB classification was used and majority of patients had M2, M3, M4, M6, and M7, which was similar to Goubin *et al.* [1].

Treatment protocol has evolved from year 1990 to 2010 for both ALL and AML. The EORTC protocol was changed to UKALL protocol in ALL. Response to steroid, TWC at presentation $> 100 \times 10^9/L$, age ≥ 10 years at diagnosis, T-cell subtype, CSF involvement at diagnosis and male gender were considered a high risk group. Unfortunately, minimal residual disease (MRD) and cytogenetics tests were not performed locally as part of the risk assessment. Those who died were due to acute event such as septicaemia in 108 patients (87%), followed by intracranial bleeding in 10 cases (8%) and major complications such as disseminated intravascular coagulation (DIVC) in 6 cases (5%).

Overall Survival Rates for ALL and AML

The immediate OS rate for acute leukaemia in Hospital USM at 3 months after diagnosis was 85.9%. For ALL, immediate OS rate at 3 months after diagnosis was 89.3%. The immediate OS rate for AML at 3 months after diagnosis was 78.0%. Overall median survival time was 20 (95% CI: 1.4 - 38.5) months. ALL had better OS rate compared to AML. These finding were also comparable to the other studies in developing countries [2,5,15,16] but considered lower to developed countries [13].

Event Free Survival (EFS) for ALL and AML

There were a few reasons for relatively lower survival of both ALL and AML in our study compared to developed countries. Our patients' cohort had different biological features. There was higher incidence of T-cell subtype (20.5%) compared to EORTC 58881 trial which possessed 7.6-15% patients with T-cell immunophenotype [1,2,17,18]. Many patients from our cohort had high TWC at the time of diagnosis. There were 21.4% with initial TWC $> 100 \times 10^9/L$ compared to 13% in EORTC 58881 study [17], and 19% in ALL-BFM 90 protocol study [19]. Thirty-seven percent of our patients had initial TWC $> 50 \times 10^9/L$. The rate of CSF involvement at presentation was also high (4%) as compared to other studies 1.8 - 2% [5,19]. Hence, lower proportion of children with good early response at 46.4%.

Lower survival rates in AML patients were seen in our study. The subtype M7 (18.6%) were higher compared to other study (6 - 10.6%) [1]. Cytogenetic analysis was not routinely performed and the data was not available for analysis except for Down Syndrome group. Simple Cox regression analysis showed significant prognostic factors for ALL were older age at diagnosis, higher TWC count at diagnosis, CSF involvement at diagnosis, poor and undetermined early response and high risk treatment group. In multiple Cox regression analysis, only older age group at diagnosis and undetermined early response were the significant factors. For simple Cox regression analysis of AML, the significant prognostic factors were bigger spleen size at diagnosis and treatment group AML BFM 87. These 2 factors showed significant results after multiple logistic regression analysis.

The present study possessed a few limitations. Firstly, the total numbers of sample size are low. About 15% (n=51) cases were excluded due to multiple reasons. As this was a retrospective record review, poor documentation in the case notes resulted in the unavailability of important information for the study. Secondly, prognostic factors such as cytogenetic abnormality especially in AML were not analysed in this study due to unavailability of cytogenetic test in the first 10-year study period. We did not investigate the MRD status after induction course. Other factors such as determination of platelet, haemoglobin counts, uric acid level, nutritional status during treatment, risk of getting infection and the distance from hospital could be considered important information for data capture in our settings. These factors might contribute to

treatment interruption which lead to poor disease outcome. Thirdly, obtaining the data retrospectively were challenging due to extensive data search in each patient treated for leukaemia. It was time consuming to recover the data accuracy for one study subject.

It is hoped that with more passionate explanation by the treating specialist, more awareness about leukaemia among family members and availability of cytogenetic study will improve patients' survival.

Conclusion

Survival rate in this study was comparable to developing countries but remained low compared to developed countries. ALL had better outcome compared to AML. Majority of ALL cases relapsed within 2 to 3 years, in contrast to AML relapse occurred within a year after diagnosis. Multifactorial causes have been attributed to the lower survival in our area.

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