

## Five-Year Survival Rate and the Factors for Risk-Directed Therapy in Acute Lymphoblastic Leukemia

### Abstract

**Background:** Acute lymphoblastic leukemia (ALL) has 5-year survival of more than 90% in many advanced cancer research institutes. However, advanced cancer care is not available to majority of poor in developing countries. The experience of treating such patients in a resource-scarce setting is described herewith. Of the 75 individuals studied, 11% of the children were stunted, >21% were underweight, and 16% of the under-five children had acute malnutrition. Massive hepatosplenomegaly and lymphadenopathy were present in 75% and 77% children, respectively. About 71% patients achieved complete remission (CR). A total of 30 (40%) children lived for >5 years after diagnosis and 21 (28%) of them had event-free 5 years. Weight for height for under-five children ( $P = 0.029$ ) and total count ( $P = 0.019$ ) were found to be significantly associated with deaths during induction. Weight for age ( $P = 0.024$ ), weight for height of under-five children ( $P = 0.009$ ), and lymphadenopathy ( $P = 0.049$ ) had a strong association with 5-year event-free survival. Using multivariate model, only weight for height among under five remained significantly associated with induction deaths ( $P = 0.021$ ) and absence of lymphadenopathy with event-free 5-year survival ( $P = 0.042$ ). **Context:** ALL has 5-year survival of >90% in many advanced cancer research institutes. However, advanced care is not available to majority of poor in the periphery of developing countries. Data available on the survival and the factors affecting the outcome among patients treated in poor resource settings are limited. **Aims:** This study aims to find the 5-year survival rate and the factors for risk-directed therapy in the region. **Settings and Design:** Cross-sectional analytical study at a tertiary center of public health in central Kerala. **Subjects and Methods:** Retrospective analysis of case sheets of 75 children who were treated at the institute from March 2006 to March 2011. **Statistical Analysis Used:** Univariate and Multivariate analysis using IBM SPSS Statistics for Windows, Version 20.0. **Results:** Of the 75 individuals studied, 11% of the children were stunted, >21% were underweight, and 16% of the under-five children had acute malnutrition. Massive hepatosplenomegaly and lymphadenopathy were present in 75% and 77% children, respectively. About 71% patients achieved CR. A total of 30 (40%) children lived for >5 years after diagnosis and 21 (28%) of them had event-free 5 years. Weight for height for under-five children ( $P = 0.029$ ) and total count ( $P = 0.019$ ) were found to be significantly associated with deaths during induction. Weight for age ( $P = 0.024$ ), weight for height of under-five children ( $P = 0.009$ ), and lymphadenopathy ( $P = 0.049$ ) had a strong association with 5-year event-free survival. Using multivariate model, only weight for height among under five remained significantly associated with induction deaths ( $P = 0.021$ ) and absence of lymphadenopathy with event-free 5-year survival ( $P = 0.042$ ). **Conclusions:** Overall survival was 40% and event-free survival was 28%. Children with acute malnutrition and a higher white blood cell count were more likely to die during induction. Underweight children, malnourished children, and children with lymphadenopathy had significantly poor chances of surviving 5 years' event free.

**Keywords:** Acute lymphoblastic leukemia, Kerala, risk-directed therapy, survival

### Introduction

5-year overall survival of acute lymphoblastic leukemia (ALL) is >90% at many advanced centers.<sup>[1,2]</sup> In India, survival rates vary from 36% to 53%, reflecting limitations in health care, differences in general health, and probably

the biology of ALL.<sup>[3-5]</sup> Treatment of leukemia had been marked by risk factors whose prognostic utility has decreased with development of specific diagnostic modalities. Unfortunately, many cases do not possess features known to warrant such specific therapy.<sup>[6,7]</sup> Further, few of the cytogenetic and molecular studies are outside scope of many cancer treating centers in developing countries.<sup>[8,9]</sup> Hence,

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**Bibin Varghese,  
Austoria Abzalón  
Joobomary<sup>1</sup>,  
P Savida**

Department of Paediatrics,  
Institute of Child Health,  
<sup>1</sup>Department of Community  
Medicine, Government Medical  
College, Kottayam, Kerala,  
India

### Address for correspondence:

Dr. Bibin Varghese,  
Poikayil, Neethi Nagar 32-A,  
Pattathanam Post Office,  
Kollam - 691 021, Kerala,  
India.  
E-mail: bibinvarghese92  
@hotmail.com

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generalized methods of risk assessment are valid in these parts of the world. This study aims to find 5-year survival and factors for risk-directed therapy in the region.

## Subjects and Methods

Data were obtained from case records of all children who were diagnosed of ALL and treated at the institute from March 2006 to March 2011 and were analyzed. Children referred to higher center, children whose details were not available for the entire period studied, and those who denied consent to participate in the study were excluded from the study. Diagnosis of ALL was confirmed by examination of bone marrow aspiration specimen. Cytochemistry (sudan black, PAS, MPO) was done in all cases. Immunohistochemistry which was not available at the hospital could be performed only in a handful of patients who were willing to do it outside. Cytogenetic studies were outside the reach of our institute.

Personal details such as age at diagnosis, sex, and socioeconomic status (Kuppuswamy classification);<sup>[10,11]</sup> anthropometric measures such as height for age, weight for age, and weight for height; clinical features such as lymphadenopathy (any patient with >one palpable lymph node >2 cm in size was considered to have lymphadenopathy), massive hepatosplenomegaly (massive hepatosplenomegaly includes either massive hepatomegaly and/or massive splenomegaly, both defined clinically, a massive hepatomegaly defined as lower border of liver palpable >five fingerbreadths below the right costal margin and massive splenomegaly defined as spleen crossing the umbilicus), mediastinal mass (supported by X-ray/computed tomography reports), central nervous system (CNS) involvement (defined as cerebrospinal fluid pleocytosis and/or cranial nerve palsies); laboratorial characteristics such as white blood cell (WBC) count at presentation, platelet count at presentation, hemoglobin count at presentation, French-American-British (FAB) class, and immunophenotype were available from the case records.

There was no definite hospital protocol on the chemotherapeutic regimens to be followed, and patients were treated using one of the three protocols summarized in Table 1. Bone marrow examination was done at the end of first induction cycle to assess response to chemotherapy. The absence of clinical evidence of disease with a blast count < five percent in the background of a normocellular marrow was defined as complete remission (CR). Deaths during induction, complications, number of relapses, years of survival, and cause of death were documented after serial study of individual's case records and other hospital records (cancer registers, inpatient/outpatient records).

The data collected were entered in Microsoft Excel 2007, Version 12.0 (Redmond, WA: Microsoft Corp.), and further analysis was done in IBM SPSS Statistics for Windows, Version 20.0 (Armonk, NY, USA: IBM Corp.). Age, WBC count, platelet count, and hemoglobin were logarithmically transformed and treated as continuous variables. Socioeconomic classification was based on Kuppuswamy's socioeconomic status scale revision for 2011.<sup>[10,11]</sup> Height for age, weight for age, and weight for height (for under five) were computed using revised IAP growth charts 2015 (weight for height of children >5 years had a different categorization as per IAP charts 2015 and was therefore excluded).<sup>[12]</sup>

Frequencies of all variables were studied to understand the characteristics of the disease in the population. Associations between variables and CR and between variables and induction deaths were also studied. Event-free survival at 5 years was defined as the absence of events (induction failure, deaths during induction, relapse, or death during remission) for the entire 5-year period studied. Variables were also studied for their association with event-free survival at 5 years. All associations were examined on cross tabs using Pearson Chi-square test and Fischer's exact test. To make study of associations more meaningful, height for age, weight for age, and weight for height were transformed into two classes (two standard deviations below normal and above). Weight for height and immunophenotype were censored to exclude "no data available" categories.

**Table 1: Drugs used in various treatment protocols used to treat acute lymphoblastic leukemia**

Protocols	Triple IT	BFM protocol III A	MCP 841
Induction	Vincristine, prednisolone, l-asparaginase (adriamycin/cyclophosphamide in high-risk patients)	Vincristine, prednisolone, l-asparaginase, cyclophosphamide, cytarabine, daunorubicin, methotrexate	I <sub>1</sub> Prednisolone, Vincristine, Methotrexate, L-asparaginase, daunorubicin I <sub>2</sub> Mercaptopurine, cyclophosphamide, methotrexate
CNS prophylaxis	Intrathecal cytarabine, hydrocortisone and methotrexate	Cranial irradiation, intrathecal methotrexate	Cranial irradiation, intrathecal methotrexate
Reinduction	-	Same as induction	Same as I <sub>1</sub>
Maintenance	Daily mercaptopurine, weekly methotrexate, monthly vincristine and prednisolone, triple IT on alternate months	Daily mercaptopurine, weekly methotrexate, monthly vincristine, and prednisolone	Vincristine and daunorubicin on day1, L-asparaginase on days 1, 3, 5 and 7, daily mercaptopurine*, weekly methotrexate'

Mercaptopurine \*3 weeks out of every 4 weeks for a total of 12 weeks, methotrexate' once a week, missing every 4<sup>th</sup> week for 12 weeks

Variables which were found statistically significant in univariate analysis were further analyzed using logistic binary regression for multivariate analysis.

## Results

Of the seventy-five individuals studied, 82.7% had age between 1 and 9 years, the median age of presentation being 4 years [Table 2]. Males contributed to two-third of the study population. About 11% of the children were stunted and >21% were underweight. Sixteen percent of the under-five children had acute malnutrition with four among them having severe acute malnutrition. Massive hepatosplenomegaly and lymphadenopathy were present in 56 (74.7%) and 58 (77.3%) children, respectively. Mediastinal mass was found in eight percent and CNS involvement in four percent of the cases. Fifty-nine percent belonged to FAB class ALL L<sub>1</sub>, forty percent to ALL L<sub>2</sub>, and one percent to ALL L<sub>3</sub> [Table 3].

At the end of first induction cycle, 53 (70.7%) patients achieved CR [Table 4]. Thirteen children died during induction due to hemorrhage and/or infections and one

child died due to hepatitis. Among the 29 (38.7%) patients who relapsed, one had testicular relapse, four had CNS relapse, and rest had bone marrow relapse. Fifteen children died during relapse, the single most important cause being infection. To be also noted are the 17 children who died during remission; infections alone lead to death in ten of these children, 3 died due to bleeding and infections, while 4 died due to other causes (hemorrhage – 1, hepatitis – 1, hemorrhage and congestive cardiac failure (CCF) – 1, and infections and CCF – 1). A total of 30 (40%) children lived for >5 years after diagnosis and 21 (28%) of them had event-free 5 years.

## Univariate analysis

None of the parameters studied had a statistically significant association with the CR [Table 5]. Weight for height for under-five children ( $P = 0.029$ ) and total count ( $P = 0.019$ ) were found to be significantly associated with deaths during induction [Table 6]. Children with acute malnutrition and a higher WBC count were more likely to die during induction. Age, sex, socioeconomic class, height for age, weight for age, clinical, and laboratorial characteristics other than total count did not have a significant effect on induction deaths.

Weight for age ( $P = 0.024$ ), weight for height of under-five children ( $P = 0.009$ ), and lymphadenopathy ( $P = 0.049$ ) had a strong evidence of association with 5-year event-free survival [Table 7]. Underweight children, malnourished children, and children with lymphadenopathy had significantly poor chances of surviving 5 years' event free. Age, sex, socioeconomic class, height for age,

**Table 2: Clinical characteristics of 75 previously untreated patients at presentation**

Characteristics	Total number 75 (100%)
Age (years)	
<1	5 (6.7)
1-9	62 (82.7)
≥10	8 (10.7)
Sex	
Male	47 (62.7)
Female	28 (37.3)
Height for age	
<1 <sup>st</sup> percentile/severely stunted	6 (8.0)
1-3 <sup>rd</sup> percentile/stunted	2 (2.7)
3-50 <sup>th</sup> percentile	46 (61.3)
50 <sup>th</sup> -97 <sup>th</sup> percentile	19 (25.3)
≥97 <sup>th</sup> percentile	2 (2.7)
Weight for age	
<1 <sup>st</sup> percentile/severely underweight	9 (12.0)
1-3 <sup>rd</sup> percentile/underweight	7 (9.3)
3-50 <sup>th</sup> percentile	49 (65.3)
50 <sup>th</sup> -97 <sup>th</sup> percentile	9 (12.0)
≥97 <sup>th</sup> percentile	1 (1.3)
Weight for height (under 5)	
<1 <sup>st</sup> percentile/severe acute malnutrition	4 (5.3)
1-3 <sup>rd</sup> percentile/moderate acute malnutrition	8 (10.7)
3-50 <sup>th</sup> percentile	26 (34.7)
50 <sup>th</sup> -99 <sup>th</sup> percentile	9 (12.0)
≥99 <sup>th</sup> percentile/obese	2 (2.7)
Lymphadenopathy	58 (77.3)
Massive hepatosplenomegaly	56 (74.7)
Mediastinal mass	6 (8.0)
CNS involvement	3 (4.0)

CNS – Central nervous system

**Table 3: Laboratorial characteristics of 75 previously untreated patients at presentation**

Characteristics	Total number 75 (100%)
Total count (per mm <sup>3</sup> )	
<10,000	40 (53.3)
10,000-50,000	23 (30.7)
>50,000	12 (16.0)
Platelet count (per mm <sup>3</sup> )	
<10,000	2 (2.7)
10,000-100,000	54 (72.0)
>100,000	19 (25.3)
Hemoglobin (per mm <sup>3</sup> )	
≤6	27 (36.0)
>6-≤8	19 (25.3)
>8	29 (38.7)
FAB class	
ALL L <sub>1</sub>	44 (58.7)
ALL L <sub>2</sub>	30 (40.0)
ALL L <sub>3</sub>	1 (1.3)
Immunophenotype*	
Pre B-cell	5 (6.7)
T-cell	4 (5.3)

\*Immunophenotype results were available only for 9 children. ALL – Acute lymphoblastic leukemia; FAB – French-American-British

clinical characteristics other than lymphadenopathy, and laboratorial characteristics did not have a significant impact on the 5-year event-free survival.

### Multivariate analysis

When the significant factors from univariate analysis were studied using multivariate model, only weight for height among under five remained significantly associated with

**Table 4: Frequency of various events among the 75 children studied**

Events	Total number 75 (100%)
Complete remission	53 (70.7)
Deaths during induction	13 (17.3)
Hemorrhage and infections	9
Infections	2
Hemorrhage	1
Hepatitis	1
Relapse	29 (38.7)
Deaths during relapse	15 (20.0)
Infections	8
Seizures	3
Hemorrhage and infections	2
Hemorrhage	1
Infections and CCF	1
Deaths during remission	17 (22.7)
Infections	10
Hemorrhage and Infections	3
Hemorrhage	1
Hepatitis	1
Hemorrhage and CCF	1
Infections and CCF	1
Overall survival (5 years)	30 (40.0)
Event free survival (5 years)	21 (28.0)

CCF – Cleveland clinic foundation

**Table 5: Relationship of various characteristics to complete remission**

Characteristics	Univariate <i>P</i> value
Age	0.301
Sex	0.437
Kuppuswamy class	0.186
Height for age	0.170
Weight for age	0.133
Weight for height under 5	0.096
Lymphadenopathy	0.061
Massive hepatosplenomegaly	0.270
Mediastinal mass	0.237
CNS involvement	0.347
Total count	0.588
Platelet count	0.560
Hemoglobin	0.739
FAB class	0.285
Immunophenotype	0.167
Treatment regimen	0.550

CNS – Central nervous system; FAB – French-American-British

induction deaths ( $P = 0.021$ ). Similarly, only absence of lymphadenopathy was found to be significantly associated with event-free 5-year survival ( $P = 0.042$ ).

### Discussion

Leukemia treatment in developing countries is peculiar for number of reasons. Clinical variances, adverse socioeconomic, cultural, and political influences make establishment of resources, procurement of drugs, and timely intervention difficult. Even when the most advanced centers of cancer care have survival >90%,<sup>[1,2]</sup> they seem distant to the poor resource settings in developing countries. However, recently, specialized centers of cancer care within

**Table 6: Relationship of various characteristics to induction deaths**

Characteristics	Univariate <i>P</i> value
Age	0.501
Sex	0.419
Kuppuswamy class	0.769
Height for age	0.421
Weight for age	0.103
Weight for height under 5	0.029
Lymphadenopathy	0.389
Massive hepatosplenomegaly	0.572
Mediastinal mass	0.061
CNS involvement	0.560
Total count	0.019
Platelet count	0.464
Hemoglobin	0.648
FAB class	0.328
Immunophenotype	0.444
Treatment regimen	0.485

CNS – Central nervous system; FAB – French-American-British

**Table 7: Relationship of various characteristics to event-free survival**

Characteristics	Univariate <i>P</i> value
Age	0.817
Sex	0.188
Kuppuswamy class	0.798
Height for age	0.282
Weight for age	0.024
Weight for height under 5	0.009
Lymphadenopathy	0.049
Massive hepatosplenomegaly	0.239
Mediastinal mass	0.458
CNS involvement	0.633
Total count	0.061
Platelet count	0.443
Hemoglobin	0.259
FAB class	0.597
Immunophenotype	0.278
Treatment regimen	0.602

CNS – Central nervous system; FAB – French-American-British



India have started showing promising results.<sup>[13,14]</sup> Recently, specialized many refuse referrals to these centers as they cannot afford to move to such locations and that it would mean not being able to simultaneously support family back home.

The multitude of factors previously described often leads to a late diagnosis of the disease. In addition, potential genetic differences and biology of ALL also contribute to the clinical picture at presentation. This study shows that males are more affected than females with a ratio of 1.7:1. The median age of presentation was found to be 4 years, a year higher than that described in western literatures.<sup>[1]</sup> However, contradictory to the popular teachings, age was not directly associated with 5-year event-free survival. This is however in line with drawings from Indian studies,<sup>[8]</sup> opening the question whether age should be considered as factor for risk stratification in our population. Age and sex also did not show any associations with treatment response and deaths during induction.

Kuppuswamy classification was the tool used to categorize socioeconomic class. All children belonged either to the lower/upper lower, middle/lower middle, and upper middle classes of Kuppuswamy classification. Lower/upper lower made 55% of the individuals. The data show that even for the upper middle class (15%), ours was the only treatment available/accessible. However, socioeconomic status did not have any significant effect on the outcomes.

Nutritional factors and concurrent infections are among the important factors adversely affecting survival in developing countries. They also influence toxicity of therapy due to effects on drug metabolism and excretion.<sup>[15-18]</sup> A significant effort was made to study this relationship in our series. Results suggest that under-five children with acute malnutrition were more likely to die during induction and have poor chances of surviving 5 years' event free. Children who were underweight also showed similar association with event-free 5-year survival.

Almost 80% of the children had lymphadenopathy and about 75% of them had massive hepatosplenomegaly. Hepatomegaly had long been included as a risk factor in BFM protocols; however, lymphadenopathy, being less common, had not been studied.<sup>[3]</sup> Our study shows significant association between absence of lymphadenopathy and event-free 5-year survival. Whether this lymphadenopathy is the result of delayed diagnosis or due to the genetic, environmental, or biologic variations in the population remains unclear. Mediastinal mass and CNS involvement were found to be less frequent in our setting. Mediastinal mass, CNS involvement, and massive hepatosplenomegaly were not found to have a significant effect on outcomes.

The proportion of patients with total count >50,000 remained comparable to other studies.<sup>[3]</sup> Although there

was a trend that total count >50,000 was associated with decreased event-free 5-year survival, it was not found to be significant ( $P = 0.061$ ). However, a high total count at presentation was significantly associated with deaths during induction. Such trend was previously described, in the study by Rubnitz *et al.* at St. Jude hospital.<sup>[19]</sup> Platelet count, hemoglobin, and FAB class were not found to have significant effect on treatment response, induction deaths, or survival.

Immunophenotyping results could be obtained only for 9 patients during the period studied. Among the available nine, four had T-cell ALL. This suggests higher proportion of T-cell ALL in Kerala, like in other parts of the country.<sup>[4,8,20,21]</sup>

Three treatment regimens were simultaneously used during the 5 years studied. None superior in terms of response to treatment or event-free 5-year survival. Each one contributed roughly the same to induction deaths.

The multitude of factors impeding the treatment had resulted in decreased survival rates compared to advanced centers within India and the world. Patients who achieved remission were considerably less (70%) and induction deaths were substantially high (17%). Study of the characteristics of leukemia shows that the population is much different from their western counter parts. And thus, foreign protocols need to be tailored considering the differences in our population, to increase survival and decrease toxicity. Further studies on the clinical and laboratorial characteristics of the disease and their associations with survival and toxicity are essential for formulating such modifications. Amid the adverse factors, an overall survival of 40% at 5 years, in a poor resource setting, is inspirational to further provide quality cancer care. By making specialized healthcare more accessible and giving financial support to needy, we can improve the life of many more. Twinning has been described as one other strategy to improve cancer care in developing countries.<sup>[5,22,23]</sup> This can also be tried within the country to make cancer care more accessible.

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### Conflicts of interest

There are no conflicts of interest.

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