Section: Paediatrics

Original Research Article

OUTCOME OF CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA 5 YEARS AFTER DIAGNOSIS – A CROSS SECTIONAL STUDY

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Abstract

Background: Acute lymphoblastic leukaemia (ALL) is the most prevalent malignancy in children and has a favourable prognosis when well treated. The prognosis is influenced by several parameters, including age, gender, white blood cell (WBC) count, CD10, French-American-British (FAB) classification, and other variables. **Aim:** Determining the prognosis of children diagnosed with acute lymphoblastic leukaemia 5 years following diagnosis **Materials and Methods:** All children who were diagnosed and treated for ALL at the Department of Paediatrics, Institute of Maternal & Child health from January 2008 to September 2012 were studied for the outcome analysis. Children and their parents were contacted for the data on the outcome of treatment. Details regarding socio-demographic data, clinical profile, treatment data, complications, and outcome were recorded in a semi structured proforma. The outcome was defined as overall survival and event-free survival (without relapses) after 5 years of diagnosis of ALL. **Result:** In the study population, there were 112 (72.3%) children with ALL-L2 and 43 (27.7%) with ALL-L1. There were no cases of ALL-L3. Out of the 155 children, 11(7.1%) had Pre-B cell ALL, 141(91%) had B cell ALL and 3 (1.9%) children had T cell ALL on flow cytometric analysis of peripheral blood or bone marrow aspirate. There were 73 ALL-L2 cases among the survivors (69.5%). Children with ALL- L2 had the highest mortality rate (65.1%).There was no statistical association with the overall or event-free survival ($p>0.05$). Most survivors (93) had an ANC below 500 cells/mm^3 (88.5%).Mortality was highest in children who had neutropenia (ANC< 500 cells/mm^3) at presentation, 34.04 ± 5.061 months [95% CI: 24.12-43.96].This was statistically associated with the overall and event-free survival ($p=0.007$). Majority (55) survivors had a haemoglobin value of 7 to 11 mg/dl (52.3%). Lowest survival (12.3%) was seen in children who had a normal haemoglobin level at presentation (HB >11 g/dl), 41.048 ± 5.856 months [95% CI: 29.56-52.52].This was not statistically significant ($p>0.05$). Maximum (93) survival was seen in children with B cell ALL (93.3%). There was significant association between overall survival and immunophenotype ($p=0.037$). **Conclusion:** The overall and event free survival rate in acute lymphoblastic leukemia in children in our institute after 5 years of diagnosis is 67.7%. B cell ALL is associated with the highest survival rate. Absolute neutrophil count less than 500 cells/mm^3 at presentation is associated with increased mortality.

INTRODUCTION

Leukemias constitute the most common group of childhood cancers worldwide and in India, with a relative proportion varying between 25 and 40%. Sixty to eighty-five percentage of all cases of leukemia reported are acute lymphoblastic leukemia (ALL). The incidence of childhood ALL is approximately 3-4 cases per 100,000 children under the age of 15 years. Overall, males experience a slightly higher leukemia risk than females. There is a significant peak in childhood ALL incidence that occurs between the ages of 3 and 5 years. Compared to the developed world, the biology of ALL appears different in India, with a higher proportion of T-Cell ALL, hypodiploidy and translocations [t(1;19),

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t(9;22), and t(4;11)]; all of which contribute to a poorer prognosis of ALL.[1]

Modern treatment strategies, consisting of intensive chemotherapy and cranial irradiation, have remarkably improved the survival of children with ALL. Despite the fact that there is improving survival among children with ALL over years, there is much work to be done as these children have long-term morbidities of treatment. Many of the children with ALL who are cured by current therapies are over treated and thus unnecessarily exposed to the risk of short and long-term adverse effects. These adverse health-related outcomes that manifest months to years after completion of treatment include organ dysfunction, second malignancies, and adverse psychosocial sequelae. Few complications of leukemia therapy are as devastating as a second cancer.[2] Subgroups of children with ALL, including infants, those with unfavorable genotypes, and those who do not have a complete remission initially or who relapse after a remission still have an extremely poor prognosis. Further intensification of existing therapies is unlikely to improve the cure rate substantially in these populations.[3] The age-adjusted incidence rate of ALL in the United States is 1.77 per 100,000 individuals per year.[4] Studies from India have reported that ALL accounted for 60 to 85% of all childhood leukemias. The median age at diagnosis for ALL is 14 years, with 58.8% of patients diagnosed at younger than 20 years of age. In contrast, 25.5% of cases are diagnosed at 45 years or older and only approximately 11% of patients is diagnosed at 65 years or older. ALL represents 75% to 80% of acute leukemias among children.[5] In virtually all cases, the etiology of ALL is unknown, although several genetic and environmental factors are associated with childhood leukemia. Although the exact causes of ALL remain elusive, laboratory advances in the analysis of chromosome structure and, more recently, high-throughput genomic approaches have demonstrated 2 important findings: (1) childhood leukemia results from a multistep process associated with the acquisition of genetic alterations in the leukemic blast cells (eg: somatic changes); and (2) childhood ALL is a heterogeneous disease composed of multiple biological subgroups often classified by sentinel genetic lesions. In 85% of cases, the target cell is the immature B lymphocyte (B precursor ALL), whereas, in the remaining 15% of cases, thymic progenitor cells are involved (T cell ALL).[6] The disease is more common in children with certain chromosomal abnormalities, such as Down syndrome, Bloom syndrome, Ataxia-telangiectasia, and Fanconi anemia. Hyperdiploidy is seen in up to one-third of B-precursor cases, and high hyperdiploidy (51-65 chromosomes) is associated with a good outcome. The favorable prognosis of hyperdiploid ALL appears to correlate most strongly with gains of chromosomes 4, 10, and 17 (so-called "triple trisomy") or of chromosomes 4 and 10 (“double trisomy”).

MATERIALS AND METHODS

The study was conducted in the Paediatric Hemato-Oncology division in the Department of Paediatrics at Institute of Maternal & Child health, Government medical college, Kozhikode from September 2016 to August 2017. The study was a descriptive cross-sectional study on the outcome of children with acute lymphoblastic leukemia 5 years after diagnosis. Written consent was obtained from the parents regarding the willingness to participate in the study. In the case of older children, verbal assent was taken from the children. All children who were diagnosed and treated for ALLat the Department of Paediatrics, Institute of Maternal & Child health from January 2008 to September 2012 were studied for the outcome analysis. Children and their parents were contacted for the data on the outcome of treatment. Details regarding socio-demographic data, clinical profile, treatment data, complications, and outcome were recorded in a proforma prepared for the study from patient records. The outcome was defined as overall survival and event-free survival (without relapses) after 5 years of diagnosis of ALL.

Inclusion Criteria

- All children who were diagnosed and treated for ALL atleast 5 years prior to the study period.
- Parental consent obtained for inclusion in the study.

Exclusion Criteria

- Children with the history of any other malignancy in the past.
- Children with pre-existing chronic medical illnesses including neuropsychiatric illnesses.

Statistical Analysis

Data collected was entered into the excel data sheet and analyzed using the PASW Statistics 18 (SPSS) software. Categorical variables are expressed in proportions and percentages. Continuous variables are expressed in means and standard deviation. Chi-square test was used to study association. Overall and event-free survival was estimated by Kaplan-Meier analysis and compared using log-rank test. A p value < 0.05 was considered significant.

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RESULTS

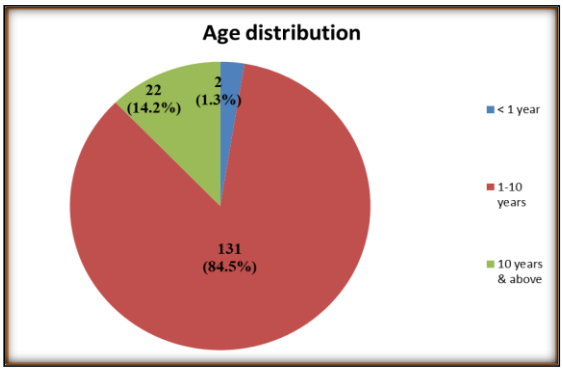

Figure 1: Age distribution of study subjects (n=155)

During the period from January 2008 to September 2012, 155 children were diagnosed and treated for ALL in the Hemato-Oncology division, Department of Paediatrics, Government Medical College, Kozhikode. Out of the 155 children, 105 (67.7%) children were alive after 5 years of diagnosis. There were 50 deaths (32.3%) within the 5 years of diagnosis. Of the 155 children, 2 (1.3%) were below 1 year of age, 131 (84.5%) children belonged to 1-10 years of age and 22 (14.2%) children were 10 years and above.

The study population consisted of 97 (62.6%) boys and 58 (37.4%) girls.

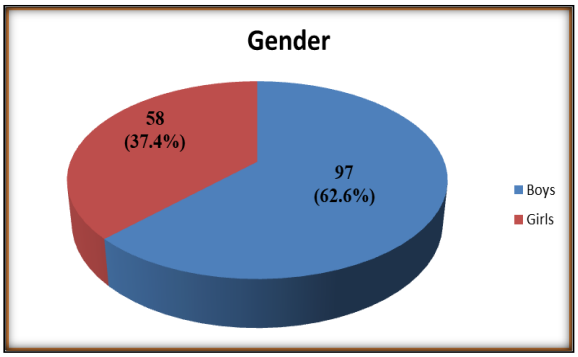

Figure 2: Gender distribution of study subjects (n=155)

Majority (79) were diagnosed and initiated on treatment between 1 to 3 months of onset of symptoms (51%) and 70 (45.2%) were diagnosed within 1 month of onset of symptoms. Six children had a delayed diagnosis after 3 months of onset of symptoms (3.9%), hence treatment was delayed more than 3 months

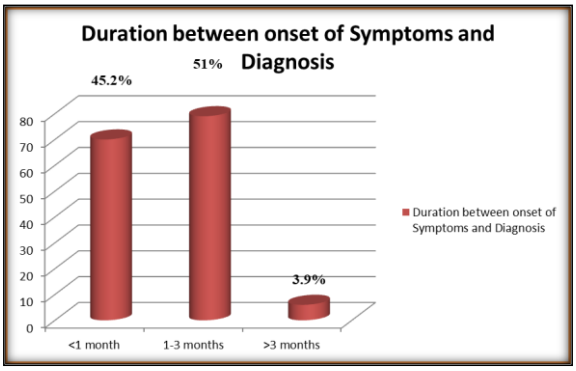

Figure 3: Duration between Onset of Symptoms and Diagnosis (n=155)

In the study population, there were 112 (72.3%) children with ALL-L2 and 43 (27.7%) with ALL-L1. There were no cases of ALL-L3.

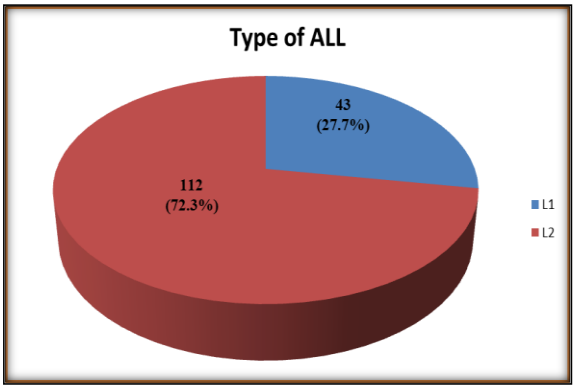

Figure 4: Type of ALL (n=155)

Out of the 155 children studied, 109 (70.3%) belonged to the standard risk group and were treated with the standard risk modified paediatric BFM protocol and 46 (29.7%) belonged to the high-risk group and were treated with the high-risk protocol.

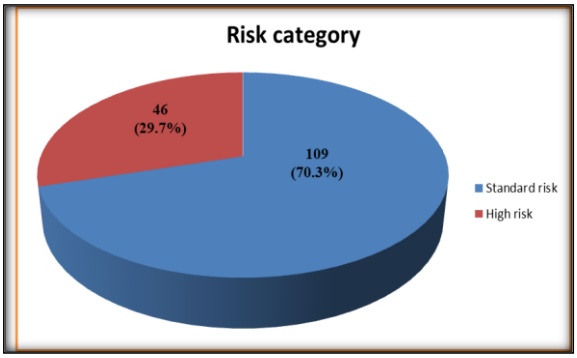

Figure 5: Risk category (n=155)

Majority of the children (90) had a total leukocyte count (TLC) between 10000-49000 cells/mm^3 (58.1%). 34 children (21.9%) had high counts of 50000 cells/mm^3 and above. 25 (16.1%) had neutropenia (absolute neutrophil count <500cells/mm^3) at presentation. 86.5% children had low haemoglobin levels with 56 children (36.1%) with haemoglobin levels less than 7 mg/dl at presentation. Thirty-one (20%) children had severe thrombocytopenia at presentation (<20,000

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cells/mm^3) and 88 (56.8%) had platelet count between 20,000 and 1 lakh cells/mm^3.

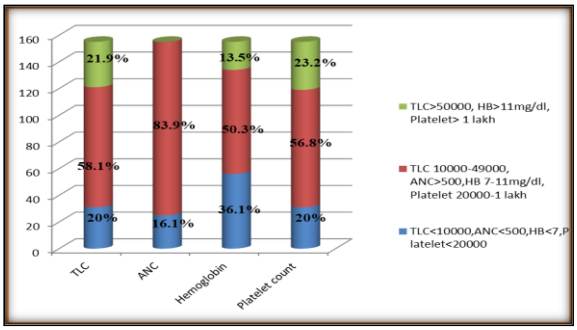

Figure 6: Investigations at Presentation (n=155)

Out of the 155 children, 11(7.1%) had Pre-B cell ALL, 141(91%) had B cell ALL and 3 (1.9%) children had T cell ALL on flow cytometric analysis of peripheral blood or bone marrow aspirate

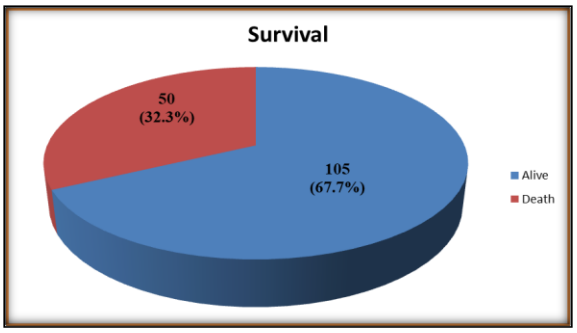

Figure 7: Survival in children with ALL (n=155)

Out of these, 40 deaths occurred in the first year of diagnosis (80%), 2 deaths in the second year (4%), 5 deaths in the third year (10%) and 3 in the fourth year (6%).There were no deaths in the fifth year from diagnosis. Majority (32) deaths occurred in the first three months of treatment (64%).

Majority of the deaths occurred before a mean period of 43.942 months (SD 1.987). Event-free survival was the same as the overall survival (67.7%) in our study. The mean survival duration was 43.94 ± 1.987 months [95 % confidence interval (CI) 40.04-47.83%].

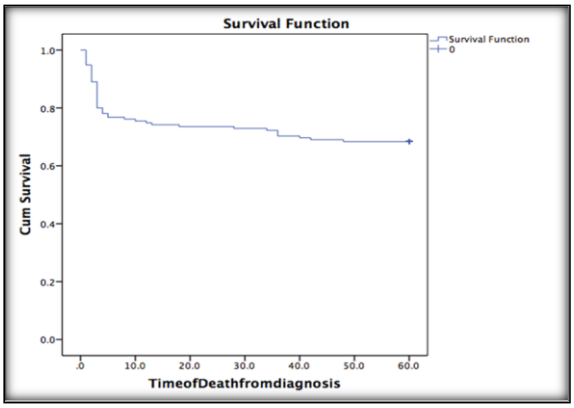

Figure 8: Kaplan Meier estimate of overall survival and event-free survival in ALL

Of the 105 survivors, 90 (85.7%) children were in the age group between 1-10 years. There was only 1 (0.95%) survivor below 1 year. Infants below 1 year of age had the highest mortality and those diagnosed between 1-10 years had the highest event-free survival, 44.36 ± 2.14 months [95% CI 40.15-48.57].There was no significant association between OS and EFS and age at diagnosis (p>0.05).

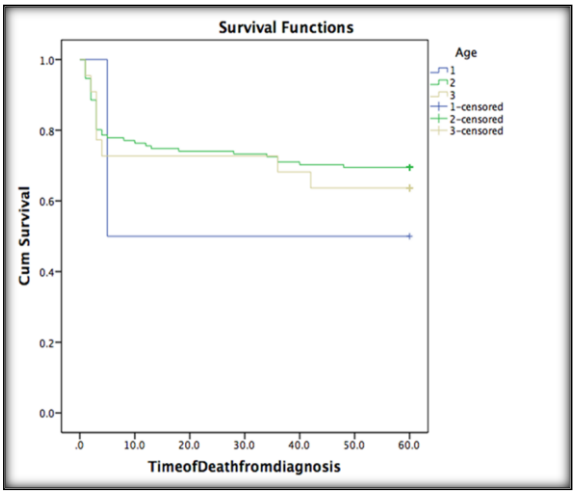

Figure 9: Kaplan-Meier paediatric ALL survival estimate by age at diagnosis

There were 65 male survivors (61.9%). Boys had higher overall and event-free survival rate than females, 44.26 ± 3.306 months [95% CI: 39.39-49.13]. This was not statistically significant (p>0.05).

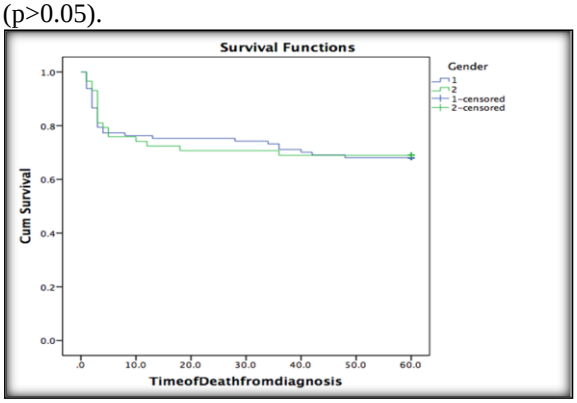

Figure 10: Kaplan-Meier paediatric ALL survival estimate by Gender

Among the 105 survivors, majority (54) were diagnosed between 1 to 3 months of onset of symptoms (51.4%). Children who were diagnosed within 1 month of onset of symptoms had the lowest survival rate. Those children diagnosed after 3 months of onset of symptoms had the highest event-free survival rate. No significant association was found between duration between onset of symptoms and diagnosis and survival (p>0.05).

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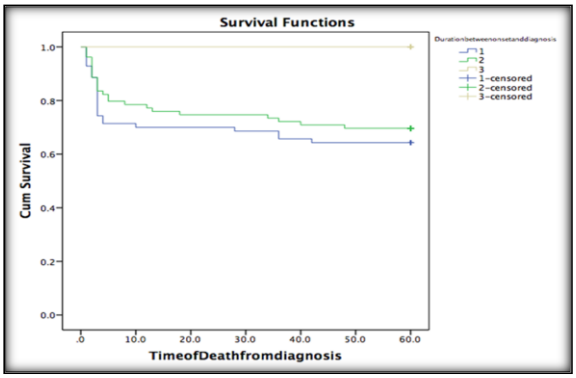

Figure 11: Kaplan-Meier paediatric ALL survival estimate by duration between onset of Illness and diagnosis

There were 73 ALL-L2 cases among the survivors (69.5%). Children with ALL- L2 had the highest mortality rate (65.1%).There was no statistical association with the overall or event-free survival (p>0.05).

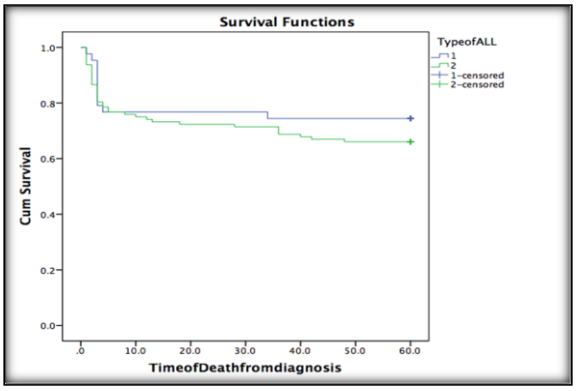

Figure 12: Kaplan-Meier paediatric ALL survival estimate by Type of ALL

Majority (77) of the survivors were standard risk patients. Children with standard-risk ALL had higher overall and event-free survival, 45.17 l ± 2.301 months [95% CI: 40.66-49.83] than children with high risk ALL. This had no statistical significance (p>0.05).

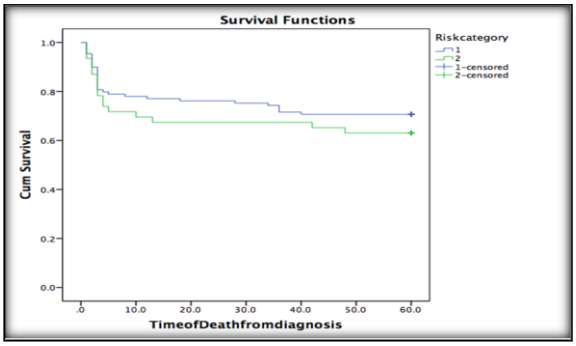

Figure 13: Kaplan-Meier paediatric ALL survival estimate by Risk Category

Majority (62) of survivors had a total leukocyte count between 10,000 to 50,000 cells/mm^3 (59%). Event-free survival was highest in children with a total leukocyte count less than 10,000 cells/mm^{3}at presentation,48.258 ± 3.757 months [95% CI: 40.89-55.62]. Mortality was highest in children with counts more than or equal to 50,000 cells/mm^3, 39.824 ± 4.538 months [95% CI: 30.92-48.71].This had no statistical association with OS or EFS (p>0.05).

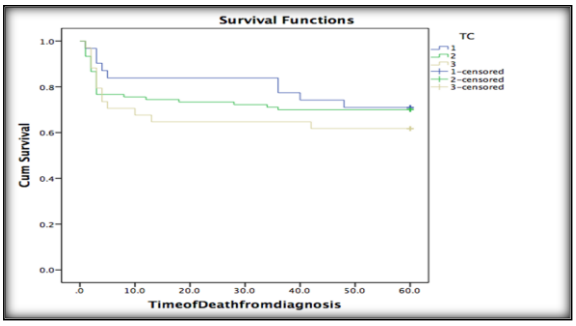

Figure 14: Kaplan-Meier paediatric ALL survival estimate by Total leukocyte Count at Presentation

Most survivors (93) had an ANC below 500 cells/mm^3 (88.5%).Mortality was highest in children who had neutropenia (ANC< 500 cells/mm^3) at presentation, 34.04 ± 5.061 months [95% CI: 24.12-43.96].This was statistically associated with the overall and event-free survival (p=0.007).

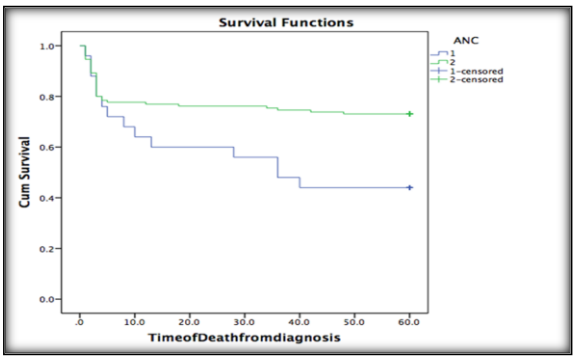

Figure 15: Kaplan-Meier paediatric ALL survival estimate by Absolute Neutrophil Count (ANC) at Presentation

Majority (55) survivors had a haemoglobin value of 7 to 11 mg/dl (52.3%). Lowest survival (12.3%) was seen in children who had a normal haemoglobin level at presentation (HB >11 g/dl), 41.048 ± 5.856 months [95% CI: 29.56-52.52].This was not statistically significant (p>0.05).

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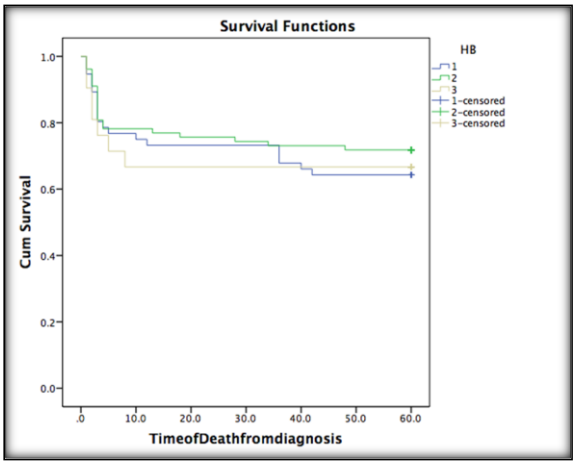

Figure 16: Kaplan-Meier paediatric ALL survival estimate by Haemoglobin (HB) at Presentation

Platelet count was between 20,000 to 100,000 cells/mm^3 in majority (57) of survivors (54.2%). Children with a platelet count between 20,000-100,000 cells/mm^3 had the lowest survival, 42.818 ± 2.714 months [95% CI: 37.49- 48.13]. Highest survival was seen in children with platelet count more than 100,000 cells/mm^3, 46.694 ± 3.702 months [95% CI: 39.43-53.95]. There was no significant association with survival (p>0.05).

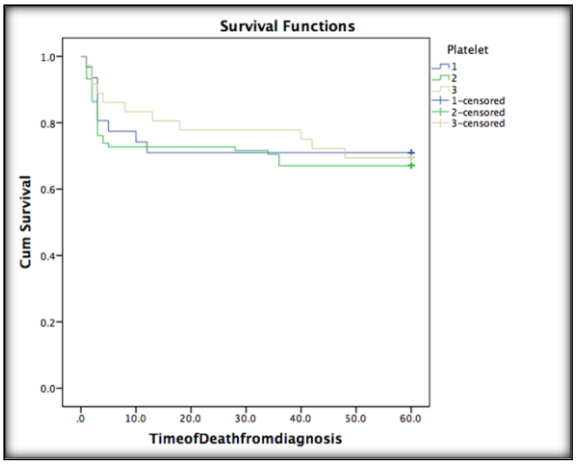

Figure 17: Kaplan-Meier paediatric ALL survival estimate by Platelet Count at Presentation

Maximum (93) survival was seen in children with B cell ALL (93.3%). There was significant association between overall survival and immunophenotype (p=0.037). [Table 1,2]

All the survivors had hepatosplenomegaly (100%) at presentation. In our study; there was no statistical association between presence of generalized lymphadenopathy, CNS involvement and mediastinal involvement with survival.[Table 3]

CSF blast was present in 12 children (7.7%) after the first lumbar puncture. There was no significant association with survival (p>0.05). [Table 4]

Of the 105 survivors, 26 (24.7%) children had received cranial irradiation as a part of their high-risk protocol. Cranial irradiation was not significantly associated with mortality (p=0.918). Majority (93) of the survivors had attained remission after induction phase of treatment (88.5%). It was not significantly associated with survival (p>0.05). All children had episodes of febrile neutropenia while on treatment (100%). Among the complications, only intracranial hemorrhage was found to be statistically associated with overall survival (p=0.003). [Table 5]

Of the survivors, 6 (5.7%) children had relapsed after induction remission. The most common site of relapse was bone marrow. Relapse of ALL after remission was significantly found to be associated with survival (p=0.006). The site of relapse was also significantly associated with overall survival (p=0.000). [Table 6]

Table 1: Immunophenotype in Subjects (n=155)

Flow cytometry	No	Percentage
Pre B cell ALL	11	7.1%
B cell ALL	141	91%
T cell ALL	3	1.9%

Table 2: Immunophenotype in Survivors (n=105)

Immunophenotype	No	Percentage
Pre-B cell ALL	4	3.8%
B cell ALL	98	93.3%
T cell ALL	3	2.8%

Table 3: Clinical Features at Presentation in Survivors (n=105)

Clinical Feature	No	Percentage	p Value
Lymphadenopathy	70	66.5%	0.356
CNS involvement	3	2.8%	0.343
Mediastinal involvement	4	3.8%	0.162

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Table 4: CSF Blast (n=105)

CSF Blast	No	Percentage
Present	7	6.6%
Absent	98	93.3%

Table 5: Complications during Treatment (n=105)

Complication	Number of Cases	Percentage	p Value
Hypertension	24	22.8%	0.324
Febrile Neutropenia	105	100%	0.146
Meningitis	3	2.8%	0.753
Hepatitis	16	15.2%	0.839
Seizures	2	1.9%	0.177
Intracranial Hemorrhage	0	0%	0.003

Table 6: Site of Relapse (n=105)

Site of Relapse	No	Percentage
Bone marrow	5	4.7%
CNS	1	0.95%

DISCUSSION

Our study was conducted in the Paediatric Hemato-Oncology division of the Department of Paediatrics, Government Medical College, Kozhikode from September 2016- August 2017. In our study, 155 children who were diagnosed with ALL from January 2008 to September 2012 were included. There are other hospital-based studies from India but they are mostly from north India. In the study by Lustosa et al, event-free survival (EFS) was 71.2 ± 5.2% (n=76) [95% confidence interval (95% CI): 62.1–82.8%] and 5-year overall survival (OS) was 72 ± 5.24% (95% CI: 62–82%).[7] In an Indian study by Radhakrishnan V et al from the Cancer Institute the EFS was 63.4%.[8] In a similar study by Kulkarni et al from PGIMER, the OS was 46% and the EFS was 43%.[9] Bajel et al from CMC, Vellore also studied ALL survivors and observed an OS of 59.8% and EFS of 56% at 5 years.[10] The OS and EFS in our study was 67.7%, which was lower than the findings by Lustosa et al but comparable to the study from south India, by Bajel et al. The lower OS and EFS observed in our study is possibly due to the inadequate infrastructural facilities during the period of treatment.

In our study 1.3% were below 1 year of age, 84.5% of children belonged to 1-10 years of age and 14.2% of children were 10 years or above. 62.6% of our subjects were boys and 37.4% were girls. In a similar study by Ching-Hon Pui et al conducted at the St. Jude's Children's Research Hospital in 247 children, 4% of children belonged to <1 year of age, 65.2% belonged to 1-10 years of age and 30.8% were 10 years of age or above.[11] This was similar to the findings from our study. In the study by Hossain et al in 14192 ALL patients, 46% of the total patients were diagnosed between ages 1 and 4 years.[12] Interestingly, the age group in which most ALL diagnoses were made was also the group that experienced the lowest mortality rate. Children who were diagnosed in infancy had the highest mortality rate This was similar to the findings in our study where children below 1 year had the least survival and those between 1-10 years had the highest survival. Age at diagnosis was a statistically significant prognostic factor for survival in the study by Lustosa et al.[7] Majority of the subjects in the study by Lustosa et al conducted at the St. Jude's Children's Research Hospital were boys (65.8%) and 35.2% were girls.[7] In our study also boys were the majority. In their study, there was no statistically significant association between survival and gender of the child. Similar findings were obtained in our study. Kulkarni et al also studied about the male preponderance in ALL.[9] But in the study by Radhakrishnan et al, gender was significantly associated with EFS possibly because females were the majority in their study.[8]

In our study majority had a delay of 1 to 3 months (30-90 days) between the onset of symptoms and diagnosis. De Angelis et al observed that the delay from onset of symptoms to diagnosis ranged from 15-29 days.[13] The relationship between time to diagnosis and survival was not statistically significant in our study. Baker et al also had a similar result.[14] Stephen et al identified in his study that immunophenotype of ALL was significantly associated with the survival.[15] Lustosa et al also identified that B ALL was significantly associated with higher EFS.[7] But in our study, we had no statistically significant association. This is probably due to the small sample size and less number of T cell ALL cases in our subjects. Lustosa et al,[7] and Radhakrishnan et al,[8] found that there were higher EFS rates in the low-risk group. But the standard risk children in our study had no significantly higher OS and EFS. Lustosa et al,[7] found no association between clinical features at presentation and survival. This was similar to what we studied. Radhakrishnan V et al from the Cancer Institute, India in their study found that total leukocyte count was significantly associated with EFS.[8] A similar finding was obtained by Lustosa et al.[7] Kulkarni et al in a study from PGIMER found that both total leukocyte count and platelet count at presentation was significantly associated with survival.[9] ANC at presentation was the only investigation that was

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significantly associated with OS and EFS in our study. Radhakrishnan et al found that survival was associated with the immunophenotype,[8] and the same finding was statistically significant in our study also. T cell ALL was significantly associated with lower survival as observed by Mukhopadhyay et al from Netaji Subhas Chandra Bose Cancer Research Institute, Kolkata.[16] The relapse rate was about 15% in the study conducted by Vaidya et al at Tata Memorial Hospital, Bombay (n=260).[17]

CONCLUSION

The overall and event free survival rate in acute lymphoblastic leukemia in children in our institute after 5 years of diagnosis is 67.7%. B cell ALL is associated with the highest survival rate. Absolute neutrophil count less than 500 cells/mm^3 at presentation is associated with increased mortality. Relapse after remission is associated with increased mortality. Children with bone marrow relapse are at more risk. Survival is not associated with socio-demographic factors, clinical findings at presentation, investigations and cranial irradiation.

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