“SOCIOECONOMIC FACTORS AFFECTING SURVIVAL IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA FROM NORTH-EAST INDIA”

Oncology

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ABSTRACT

Acute lymphoblastic leukemia (ALL) is a highly curable childhood cancer with a survival rate of nearly 80% in developed countries but is around 45% in developing countries. This retrospective study analyzed the association between demographic and socioeconomic factors with survival in pediatric ALL. All confirmed cases of pediatric ALL (age <18 years) registered at Dr. B Borooah Cancer Institute between 2010 to 2017 were analyzed using data collected from hospital-based cancer registry and case records. Seventy-five confirmed cases of pediatric ALL were eligible for the study. The median age of presentation was six years with a male: female ratio 1.9:1. Overall survival at 4-years was 43.8%, with a median survival of 25 months. A trend for higher 4-year overall survival was seen in female children (54.1% *versus* 37.9%, $p=0.097$). Patients from rural areas (44% *versus* 39.5%, $p=0.308$), with higher maternal education (83.3% *versus* 41.1%, $p=0.161$) and patients who did not abandon treatment (49.1% *versus* 31.2%, $p=0.497$) had better survival, but the differences were not significant. Four years overall survival in upper-middle, lower-middle, upper-lower, and lower class were 85.7%, 74.9%, 38.1%, and 7.7% respectively (upper-middle *versus* lower socioeconomic class, $p=0.0001$). Multivariate analyses confirmed a statistically significant relationship between socioeconomic status and survival, with the upper-middle group had a 90% decreased risk of death compared to the lower socioeconomic group. There is an urgent need for a proper definition of the problems of childhood ALL to introduce appropriate policies for improving survival in developing countries.

KEYWORDS

acute lymphoblastic leukemia, overall survival, socioeconomic status, modified Kuppaswamy scale.

INTRODUCTION:

Leukemia is the most commonly occurring childhood cancer in most industrialized and developing countries [1]. Acute lymphoblastic leukemia (ALL) has the highest cure rate amongst all the pediatric malignancies, with survival reaching nearly 80% in developed countries [2,3,4]. However, it is still a vision in developing countries with a survival rate of around 45% [5]. An Indian study that compared the survival of childhood cancer from Chennai and Bangalore with other parts of the world observed 50% lower survival rates amongst children with leukemia in this part of the world [6]. Assigned conditions for treatment, socioeconomic status, awareness, and advanced disease stage were seen to be associated with causes of poor survival [7]. Early diagnosis, easy access to quality health care, and treatment compliance are considered to be closely related to socioeconomic status. However, very few studies have specifically addressed this issue of socioeconomic factors' influence on children's prognosis with ALL, with conflicting results [8].

There is a need for including socioeconomic factors in the reports on the outcome of ALL therapeutic trials. We hypothesized that demographic and socioeconomic factors, including age, sex, areas of residence, maternal education, and socioeconomic status, might contribute to overall survival in pediatric ALL.

MATERIAL AND METHOD:

The study was a retrospective hospital-based observational study.

Objectives of the study: Our study sought to analyze the association of demographic and socioeconomic factors with survival in pediatric ALL patients.

INCLUSION CRITERIA: Newly confirmed pediatric ALL (age below 18 years) registered at Dr. B Borooah Cancer Institute from January 2010 to December 2017 were included for the analysis.

EXCLUSION CRITERIA: Patients with incomplete diagnostic

workup, previous diagnosis of other cancer, and children who received any cancer-directed treatment outside were excluded.

Diagnosis of ALL was confirmed by bone marrow aspiration examination. Immunohistochemistry was done in all cases. Cytogenetic studies was not available at the hospital could be performed only in a handful of patients who were willing to do it outside. There was no definite hospital protocol on the chemotherapeutic regimens to be followed. All patients received treatment as per the 'BFM-95 protocol' [10].

We collected variables including age, gender, areas of residence, parental occupation, parental education, and family income from the Hospital-Based Cancer Registry (HBCR). Treatment-related details were retrieved from medical case records. Following factors were analyzed: age group (age ≤ 10 years *versus* > 10 years), area of residence (rural *versus* urban), maternal education (more than secondary school education *versus* less than secondary school education), parental socioeconomic status (upper-middle, lower-middle, upper-lower, and lower class). Socioeconomic status was calculated using a modified Kuppaswamy scale [9] (Annexure 1).

Treatment outcome for each patient was categorized as: (1) completed or presently undergoing treatment; (2) abandoned treatment or loss to follow up; and (3) death from any cause.

Abandonment of treatment was defined as the failure to start or continue scheduled treatment for four or more consecutive weeks [11]. Analysis of disease outcome was examined as overall survival (OS). Overall survival was measured from the date of initial diagnosis to date of death from any cause or date of the last contact using the Kaplan-Meier method. The log-rank test was used to evaluate survival differences amongst the groups. Cox proportional hazards models were used to assess the impact of a selected variable on overall

survival. Results were expressed as adjusted hazard ratios (HRs) and corresponding 95% confidence intervals (CI). P-values less than 0.05 were considered statistically significant. All statistical analyses were performed using SPSS version 19.0.

The study received approval from the institutional ethics committee (IEC).

RESULTS:

Our institute registered a total of 592 childhood cancer patients between January 2010 and December 2017. Acute leukemia constitutes 138(23.3%) cases, with ALL comprised of 95(16%) patients. Of these, 75 patients of pediatric ALL were eligible for the study. These 75 patients consisted of 49(65.3%) boys and 26(34.7%) girls. The mean age of presentation was 6.7 years (SD 4.26), and the median age was six years. Majority of our pediatric ALL patients (n=47, 62.7%) coming from rural background; 28 cases (37.3%) from urban area. In terms of maternal educational qualifications, 68 (90.6%) children's mother had less than secondary school education. In this cohort greater part of socioeconomic status was contributed by parents with the upper-lower socioeconomic group in 38 patients (50.7%) followed by lower-middle in 17(22.7%), lower in 13 (17.3%), and upper-middle in 7(9.3%) patients. Abandonment of treatment due to various reasons was seen in 19 (25.3%) cases. It is noteworthy that this information was obtained from medical records and not from families concerned (Table 1).

Table 1: Demographic and treatment characteristics of children diagnosed with ALL

Variables		N (%)	Median (Mean±SD)
Sex	Male	49(65.3)	
	Female	26(34.7)	
Age at diagnosis (in years)	6(6.7±4.2)		
Age	≥10yrs	18(24)	
	<10yrs	57(76)	
Maternal education	More than secondary school	6(8)	
	Less than secondary school	68(90.6)	
Residence	Rural	47(62.7)	
	Urban	28(37.3)	
Modified Kuppuswamy scale score (Socioeconomic status)	Lower <5	13(17.3)	
	Upper lower 5-10	38(50.7)	
	Lower middle 11-15	17(22.7)	
	Upper middle 16-25	7(9.3)	
Treatment abandonment	Yes	19(25.3)	

In our study, the overall survival at 4-years for the entire cohort was 43.8%, with a median survival of 25 months. Survival was better in girls (4-years OS 54.1% versus 37.9%, $p=0.097$); however, the difference was not statistically significant. Survival by age group showed no difference in survival between the age group ≤ 10 years and >10 years (42.5% versus 52.5%, $p=0.123$). Place of residence was also not associated with survival as patients residing in the rural area were having overall survival 44 % compared to 39.5% in urban ($p=0.308$). To some extent, maternal education survival was higher with Higher maternal education (83.3% versus 41.1%, $p=0.161$), but significance was not seen due to fewer patients in higher maternal education groups. Patients who did not abandon treatment (49.1% versus 31.2%, $p=0.497$) were also have increased survival, but the difference was not significant (Table 2).

According to socioeconomic status in the upper-middle, lower-middle, upper-lower, and lower class, four years of overall survival were 85.7%, 74.9%, 38.1%, 7.7%, respectively (Figure 1 and Table 2). Upper middle socioeconomic class patients showed statistically significant higher survival compared to lower socioeconomic class ($p=0.0001$).

Table2: Survival analysis of children diagnosed with ALL

Variables		4-years overall survival		Overall survival ^c	
	(%)	P-value	Hazard ratio	(95%CI) ^d	
Sex	Female	54.1	0.097	1	Reference
	Male	37.9		1.124	0.506-2.498
Age at diagnosis	Age ≥ 10 yrs	52.5	0.123	1.118	0.482-2.592
	Age < 10 yrs	42.5		1	Reference
Maternal education	More than secondary school	83.3	0.161	1	Reference
	Less than secondary school	41.1		2.713	0.346-21.254
Residence	Rural	44	0.308	0.618	0.311-1.228
	Urban	39.5		1	Reference
Modified Kuppuswamy scale score	Lower ≤ 5	7.7	0.0001	1	Reference
	Upper Lower 6-10	38.1		0.332	0.147-0.750
	Lower Middle 11-15	74.9		0.120	0.033-0.436
	Upper Middle 16-25	85.7		0.108	0.013-0.912
Treatment abandoned	Yes	31.2	0.497	1.438	0.668-3.099
	No	49.1		1	Reference

- Kaplan-Meier estimates of overall survival for all acute lymphoblastic leukemia cases
- The end-point of overall survival was measured from the date of initial diagnosis to date of death from any cause or date of the last contact. Seventy-five subjects are included in the Cox regression model.
- Mutually adjusted for each other.
- Corresponding 95% confidence interval.

The multivariate analyses confirm various survival probabilities by socioeconomic status (Table 2). We found a statistically significant relationship between socioeconomic status and survival ($p=0.0001$); upper-middle socioeconomic groups had almost a 90% decreased risk of mortality than lower socioeconomic groups. Maternal education less than secondary school had an

Figure1: Kaplan-Meier estimates overall survival for all acute lymphoblastic leukemia cases by socioeconomic status (modified Kuppuswamy Scalescore). Log-rank test of heterogeneity: $\chi^2=20.96$, $P=0.0001$

increased HR compared to the reference group, the magnitude varying around 2.7-fold (overall survival), but it was not statistically significant. For income, HR was close to 1. No relationship between gender, residence, and survival was observed, both in the univariate and multivariate analyses. Treatment abandonment also did not show any trend or significant impact on survival from ALL.

DISCUSSION:

Our study found the differences in treatment outcomes between patients with the low and upper socioeconomic class were substantial. This was only a significant factor affecting survival in our observation. This concern of socioeconomic influence may be more evident in

pediatric ALL owing to the length and cost of treatment. A meta-analysis also showed that, in terms of individual-level composite SES indices, children from low SES suffered from nearly twofold higher death rates from ALL [12]. Multiple interventions are thus required to reduce the negative influence of low socioeconomic status.

There is a complicated relationship between low socioeconomic class and treatment abandonment. The various studies [13,14] suggested that strict compliance to treatment protocol is an essential determinant of treatment outcome. We also found similar things with poor survival in patients who abandoned treatment. Although it was not significant, this might be attributed to high mortality rates due to poor supportive care in hospitals in developing countries. Treatment abandonment was more frequent in patients with low socioeconomic class. Efforts should be made to reduce its magnitude, and interventions targeting these factors are likely to decrease socioeconomic gradients in the outcome. Providing free treatment, accommodation, and transport to families in a hospital in El Salvador resulted in a decrease in abandonment rates to 13% [15].

Higher maternal education thought to be improving treatment compliance leads to improved survival, as seen in a study in Norway [16]. But we did not observe any difference in survival according to maternal education. This may be due to a significantly less number of patients whose mothers have more than secondary education.

The residence has been variably reported as being associated with survival. A recent multi-national study [17] had shown that living in rural was associated with a less favorable prognosis, but it was not confirmed in other studies [18]. Our research also did not find any statistically significant difference in survival in patients coming from rural areas compared to urban. This could be linked to improvements in infrastructure, including a better mode of communication.

Although males have a higher incidence, female patients tolerate this intensive treatment well with higher survival [19]. Our observation also substantiates this showing trend for better survival in female patients as compared to males.

Our study has a significant limitation of being retrospective, which needs to be considered. Information about SES was collected from a hospital-based cancer registry where these details were entered at the time of registration by interview. Hence a reporting bias cannot be excluded, significantly income, which is not overtly discussed in our country. There were confounding factors, including high-risk genetic changes and differential chemotherapy response, which might have affected our study outcomes.

This study reported the treatment outcomes of children with ALL with attempts to explore areas requiring improvement in cancer care policy implementation. Based on our retrospective study, we recommend a program enabling parents to maintain their income level. Handicraft-programs [20] offering parents work opportunities to cover treatment costs are good examples. Universal health-insurance to all patients with food and lodging should be provided to cover all necessary expenses. These measures most likely will positively influence the adherence and treatment outcome of children with ALL.

CONCLUSION:

Our study points to the negative effect of lower socioeconomic status on children's survival suffering from ALL. Future studies should identify specific mechanisms underlying these factors and evaluate interventions aimed at improving the outcome of children with ALL with low socioeconomic status.

Annexure1: Modified Kuppuswamy Socioeconomic Status Scale

A	Education of head of the family	Score
1	Profession or Honours	7
2	Graduate or postgraduate	6
3	Intermediate or post-high school diploma	5
4	High school certificate	4
5	Middle school certificate	3
6	Primary school certificate	2
7	Illiterate	1
B	Occupation of the head of the family	Score
1	Profession	10
2	Semi-Profession	6

3	Clerical, Shop-owner, Farmer	5
4	Skilled worker	4
5	Semi-skilled worker	3
6	Unskilled worker	2
7	Unemployed	1
C	The family income per month(in Rs)	Score
1	≥19575	12
2	9788-19574	10
3	7323- 9787	6
4	4894- 7322	4
5	2936-4893	3
6	980-2935	2
7	≤979	1
	Total Score	Socioeconomic class
	26-29	Upper (I)
	16-25	Upper Middle (II)
	11-15	Lower middle (III)
	5-10	Upper lower (IV)
	<5	Lower (V)

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