

# Impact of Sociodemographic Factors and Nutrition on the Duration of Induction Phase of Chemotherapy in children with Acute lymphoblastic leukemia: A Tertiary Center Experience from North India

## Abstract

**Background:** Immunocompromised patients are at increased risk of infections, especially those living in poor hygienic conditions. **Aims and Objectives:** This study aims to assess the effect of weight, immunization status of the child at the start of treatment along with the socioeconomic status (SES), and demographic parameters, i.e., type of house, sanitary facility (SF), and source of drinking water on the duration of induction phase of chemotherapy (delayed if the patient received chemotherapy for >29 days). **Materials and Methods:** 110 pediatric acute lymphoblastic leukemia patients aged 1.5–14 years who underwent induction of remission from June 2015 to February 2018 were included. The immunization status and weight of the child were recorded at the start of treatment. SES was assessed using modified Kuppuswami scale and a questionnaire was used to determine various sociodemographic parameters. **Results:** The patients not immunized as per age ( $P = 0.000$ ) and having poor demographic parameters, i.e., mud house ( $P = 0.000$ ), absence of SF ( $P = 0.013$ ), and nonfiltered drinking water ( $P = 0.005$ ), had significant delay. The duration of induction phase of chemotherapy was not delayed with poor SES ( $P = 0.832$ ). Although the duration was delayed in patients with weight  $\geq 10$  percentile, it was not statistically significant ( $P = 0.079$ ). On analyzing the three demographic parameters together as Water-Sanitary Facility-Housing (WaSH) Score (0–4), the duration was also significantly delayed if the patients had WaSH score  $< 2$ . **Conclusion:** The duration of induction phase of chemotherapy is delayed with inadequate immunization status and poor hygiene of the child.

**Keywords:** Induction, leukemia, pediatric, socioeconomic factors

## Introduction

Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy worldwide, accounting for about 30% of all childhood malignancies.<sup>[1]</sup> According to the GLOBOCAN 2012 estimates (<http://globocan.iarc.fr/>), nearly 25,000 children in India are diagnosed with cancer each year, among which approximately 9000 children are diagnosed with acute leukemia. Although worldwide estimates for overall 5-year survival rate in ALL patients are more than 85%, exact data for the Indian population are lacking in the present literature.<sup>[1,2]</sup> A population-based cancer registry from Chennai and Bengaluru suggests a much lower cure rate in India.

According to the WHO/United Nations Children's Fund (2015), approximately 2.9 billion people worldwide have access to

improved sanitary facilities or measures to sequester human feces from the environment including pit latrines with slabs. A majority of population, i.e., around 892 million, worldwide do not have access to sanitary facilities whatsoever and practice open field defecation, rampant in rural and urban slums in South and Southeast Asia as well as Sub-Saharan Africa. India is the largest contributor of open field defecation in the world, practiced by nearly 600 million people. 844 million people worldwide lack a basic drinking water service. In India, 1.2 billion people have access to drinking water from improved sources.<sup>[3]</sup>

Various factors are responsible for lower overall as well as event-free survival rate in children with ALL in India such as delay in diagnosis, malnutrition, infections, abandonment, limited resources, as well as limited access to adequate treatment. One of the major causes of recurrent infections in

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Indian children live in poor living conditions. Although patients have access to sanitary latrines and filtered drinking water in the hospital, they lack the same at home. Furthermore, few of the patients after being discharged from hospital live in an overcrowded house made of mud, which results in a cycle of infection, hospitalization, and undernutrition. This results in prolonged hospitalization as well as delay in completion of treatment.

Previous studies have analyzed the effect of socioeconomic status (SES) of the child, parental education, and time to reach hospital for chemotherapy on the event-free as well as overall survival.<sup>[4-6]</sup> In our study, we tried to systematically evaluate the effect of sociodemographic parameters on the duration of induction phase of chemotherapy.

## Materials and Methods

After an ethical clearance from the institutional ethics committee, children with ALL who underwent induction of remission from June 2015 to February 2018 were included in the study.

A questionnaire was used to record the weight and immunization status of the child and assess the type of house, source of drinking water, and sanitary facilities before start of treatment. The following definitions were used in the questionnaire:

- (I) Type of house: (i) Brick house: House where the floor is paved, walls are stone or brick-built, and roof is made of asbestos or concrete. (ii) Mud House: House in which floor is packed earth, walls are made of dried mud or thatched, and roof is thatched or comprises slate
- (II) Source of drinking water: (i) Filtered water: Drinking water obtained from reverse osmosis purifier system installed in the household or bottled water. (ii) Nonfiltered water: Drinking water obtained from hand pump, tap, submersible pump, and well
- (III) Sanitary facility (SF): (i) SF present: The presence of pit latrine with/without pour-flush system. (ii) SF absent: Open field defecation.

Our patients received modified children's oncology group protocol. Children were stratified into standard risk and high risk based on the National Cancer Institute/Rome criteria, which include (i) age, (ii) total leukocyte count (TLC), (iii) immunophenotype, (iv) cytogenetics, and (v) central nervous system (CNS) status. Children in the standard risk group (age, 1–9 years, TLC,  $<50,000/\text{mm}^3$ , pre-B cell ALL, favorable cytogenetics, i.e.,  $t(12;21)$ , hyperdiploidy, and CNS status I) received 3-drug induction with vincristine, L-asparaginase, and intrathecal methotrexate and those in the high-risk group (age  $>9$  years, TLC,  $\geq 50,000/\text{mm}^3$ , T-cell ALL, unfavorable cytogenetics, i.e.,  $t(9;22)$ ,  $t(1;19)$ , mixed lineage leukemia rearrangement, hypodiploidy, and CNS status II/III) received 4-drug induction with vincristine, L-asparaginase, daunorubicin, and intrathecal methotrexate. For the induction phase of

chemotherapy, patients were admitted in the hospital for 10–14 days depending on their counts and clinical status, following which they were discharged to attend our day care chemotherapy clinic for further injections. Usually, it took 29 days to achieve the end of induction phase of chemotherapy. Only those patients who did not experience febrile illness during hospital stay and were stable at the time of discharge were included. We hypothesized that the adverse sociodemographic parameters result in episodes of infection causing reduction in counts and delay in completion of induction chemotherapy. The duration of induction phase of chemotherapy was considered delayed, if the patient received chemotherapy for more than 29 days. Those who died during induction or abandoned the treatment were excluded from the study.

The immunization status of the patients was assessed keeping in view of the National Immunization Schedule of India, which includes timely doses of bacillus Calmette–Guérin, hepatitis B, diphtheria–pertussis–tetanus, and measles. The patients who received the vaccines were considered immunized as per age.

Weight for age percentile of the child was determined using the WHO growth charts to divide the patients into two groups, i.e., weight for age  $<10$  percentile and weight for age  $\geq 10$  percentile. The SES of patients was assessed using Kuppuswamy Scale which includes education of the father, his occupation, and monthly income.

Apart from evaluating these parameters individually, a water-SF-housing (WaSH) score was further devised and analyzed to predict the delay in the duration of induction phase of chemotherapy. The WaSH score consisted of (i) source of drinking water (filtered water = 1 and nonfiltered water = 0), (ii) SF (present = 1 and absent = 0), and (iii) the type of house (mud house = 0 and brick house = 1), with a maximum score of 3 and a minimum score of 0.

## Statistical methods

Data management and statistical analysis was performed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA). The data were presented as mean  $\pm$  standard deviation for continuous variables and as frequency and percentage for categorical variables. Independent sample *t*-test was used to compare two groups with respect to normally distributed numerical data.  $P < 0.05$  was considered statistically significant.

## Results

One hundred and ten children of pediatric ALL with a mean age  $6.5 \pm 3.5$  years were enrolled with a male-to-female ratio of 2.6:1. Demographic characteristics of the sample population among the two groups are provided in Table 1. The duration of induction chemotherapy was delayed in 71 children with a total duration of  $\leq 36$  days in 47 children, managed on an outpatient basis for an episode of mild febrile neutropenia, and  $>36$  days in 24 children, admitted

in hospital for severe febrile neutropenia. Among the children who were admitted for febrile neutropenia, 33% had acute gastroenteritis, 32% had lower respiratory tract infection, 29% had skin and soft-tissue infections, and 6% had urinary tract infection. The most common organism isolated was *Staphylococcus aureus* (46%), followed by Gram-negative organisms (39%), i.e., *Klebsiella pneumoniae*, *Escherichia coli*, and *Pseudomonas*. Fungal sepsis contributed 15% among the isolated organisms. The patients with respiratory infections had more delay as compared to infection at other sites.

Of all the patients enrolled, 34 (30.9%) were not immunized, 40 (36.4%) were residing in mud house, 46 (41.8%) had no access to SF, and 75 (69.1%) were drinking nonfiltered water. There was a statistically significant increase in duration of chemotherapy, if the patient was unimmunized ( $P = 0.000$ ), living in a mud house ( $P = 0.000$ ), with no access to SF ( $P = 0.013$ ), and drinking unfiltered water ( $P = 0.005$ ) [Table 2].

The children belonging to lower ( $n = 50$ ) and middle ( $n = 60$ ) SES showed no significant effect on the duration of induction phase of chemotherapy ( $P = 0.832$ ). Although the delay in induction phase of chemotherapy was noted in the group with weight age percentile  $\geq 10$  ( $P = 0.079$ ), it was not significant statistically [Table 2].

A WaSH score of 0 or 1 was significantly associated with delay in duration of induction phase of chemotherapy ( $P = 0.000$ ) [Table 3].

## Discussion

Survival rates are poor in developing countries due to high treatment-related mortality (TRM) attributed partly to high prevalence of malnutrition<sup>[7]</sup> and infection. Infection is the most common cause of TRM even in developed countries. The incidence of TRM on contemporary trials in ALL is 2%–4%.<sup>[8,9]</sup> It has been postulated that malnutrition results in immune dysfunction causing poor tolerance to infections and altered drug metabolism leading to higher drug toxicity and adverse clinical outcomes.<sup>[9,10]</sup>

Several studies in developed countries have evaluated the effect of undernutrition on prognosis and survival of patients with acute leukemia. Interestingly, both undernutrition and obesity are associated with an inferior event free-survival as reported by Orgel *et al.*<sup>[11]</sup> A study from India by Roy *et al.* stated that undernourished children experience more episodes of febrile neutropenia resulting in poor outcome.<sup>[12,13]</sup> Thus, nutritional status of the child at the start of treatment correlates with outcome. In our study, however, the duration of induction was not significantly affected by the nutritional status of the child ( $P = 0.079$ ).

Apart from nutritional status, our study also focused on the influence of immunization status of the child and SES along with associated demographic factors on the duration

**Table 1: Demographic characteristics of the study sample**

Characteristics	Results
Age (years), mean $\pm$ SD	6.5 $\pm$ 3.5
Male:female	2.6:1
Nutrition, $n$ (%)	
Normal nutrition	89 (80.9)
Under nutrition	21 (19.1)
SF, $n$ (%)	
Yes	64 (58.2)
No	46 (41.8)
SES, $n$ (%)	
$\leq$ III	60 (55.5)
$\geq$ IV	50 (45.5)
Water supply, $n$ (%)	
Filtered	35 (31.8)
Nonfiltered	75 (68.2)
Type of house, $n$ (%)	
Brick house	70 (63.6)
Mud house	40 (36.4)
Immunization status, $n$ (%)	
Yes	76 (69.1)
No	34 (30.9)

SD – Standard deviation; SES – Socioeconomic status; SF – Sanitary facility

**Table 2: Effect of various parameters on the duration of induction phase of chemotherapy**

	Duration of induction	$P$
SES		
Lower ( $n=50$ )	33.32 $\pm$ 5.7	0.832
Middle ( $n=60$ )	33.42 $\pm$ 6.72	
House		
Mud house ( $n=40$ )	37.58 $\pm$ 7.78	0.000
Brick house ( $n=70$ )	30.97 $\pm$ 3.439	
Sanitary latrine		
Absent ( $n=46$ )	35.11 $\pm$ 7.87	0.013
Present ( $n=64$ )	32.13 $\pm$ 4.47	
Water supply		
Nonfiltered water ( $n=75$ )	34.5 $\pm$ 6.89	0.005
Filtered water ( $n=35$ )	30.94 $\pm$ 3.74	
Immunization status		
No ( $n=34$ )	38.85 $\pm$ 7.782	0.000
Yes ( $n=76$ )	30.92 $\pm$ 3.298	
Weight		
<10 percentile ( $n=58$ )	32.38 $\pm$ 5.57	0.079
$\geq 10$ percentile ( $n=52$ )	34.48 $\pm$ 6.86	

SES – Socioeconomic status

**Table 3: Water, sanitation, house score**

Score	Duration of induction (days)	$P$
<2 ( $n=50$ )	35.98 $\pm$ 7.71	0.000
$\geq 2$ ( $n=60$ )	31.20 $\pm$ 3.56	

of induction phase of chemotherapy. Many studies have assessed the effect of SES on the incidence of ALL as well

as its effect on overall survival and relapse, with only few studies from developing countries including India.<sup>[14-16]</sup>

In our study, children with poor living conditions, i.e., children residing in a mud house with no access to SF and filtered drinking water, had a delay in the duration of induction phase of chemotherapy. Furthermore, the delay in induction was experienced by those who were not immunized before start of induction chemotherapy ( $P < 0.001$ ). The delay was mostly due to unprecedented infections during the treatment when patients were discharged home to come for chemotherapy, resulting in deterioration of patient's general condition, requiring hospitalization and thus prolonging the duration of induction phase of chemotherapy. We hypothesize that delay in the unimmunized group may be due to associated adverse sociodemographic parameters rather than immunization alone as most of these children belonged to SES IV and V with unhygienic living conditions.

## Conclusion

Disease as well as chemotherapy weakens the immune system, predisposing patients with cancer to innumerable infections resulting in multiple hospitalizations, increasing the incidence of relapses as well as patient succumbing to fatal infections. It is already known that the delay in early phase of chemotherapy can affect overall survival. Thus, to curb delay in chemotherapy due to infectious causes and thereby improve outcome, an improvement in living conditions can play an important role. This study subjectively evaluates the living condition of patients and its effect on the duration of chemotherapy.

The authors of this study feel that interruptions during induction chemotherapy due to infections results in dose reduction/stoppage of chemotherapeutic agents during the febrile episode, causing delay in completion of induction chemotherapy. This may have an adverse effect on overall and event-free survival of patients with acute leukemia. More studies are needed to support the effect of interruption during induction chemotherapy on overall/event-free survival in patients with acute leukemia.

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## Conflicts of interest

There are no conflicts of interest.

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