National Board of Examinations - Journal of Medical Sciences
Volume 3, Issue 3, Pages 255–265, March 2025
DOI 10.61770/NBEJMS.2025.v03.i03.002

ORIGINAL ARTICLE

Correlation of Baseline Clinical Characteristics as Risk Factors for Pneumonia in Children with Acute Lymphoblastic Leukemia (ALL)

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Accepted: 20-January-2025 / Published Online: 01-March-2025

Abstract

Background: Pneumonia is a major cause of death during chemotherapy for acute leukemia. Here we are presenting the correlation of baseline characteristics and pneumonia in children with acute lymphoblastic leukemia (ALL) which affect the overall outcome of patients with ALL. **Methods:** We conducted a prospective observational study for one year and 6 months duration in which 77 pediatric patients with newly diagnosed acute lymphocytic leukemia (ALL) who underwent chemotherapy in a tertiary care hospital. **Result:** Twenty-eight of the 77 pediatric participants in the trial got pneumonia while receiving therapy. There were 41 children (53.2%) older than five years, and 36 (46.7%) less than five. 18% (14/77) of the children were T ALL, and 82% (63/77) were B ALL. The male to female ratio was 5.4:1. Of the patients, 75% (58/77) were classified as high risk and 25% (19/77) as low risk. CNS/testicular involvement occurred at some stage during treatment in 15% (12/77). Of the 37 pneumonia cases, fever was the most common presenting symptom (97%) followed by respiratory distress (60%) and ANC<500 (75%). Cough was the less frequent presenting complaint. Thus, radiographic criteria were taken into consideration in order to diagnose pneumonia. **Conclusion:** The risk factors for development of pneumonia in children with ALL were age<5yr, baseline TLC of >50,000, induction phase of chemotherapy and these were statistically significant in our study.

Keywords: Pneumonia, Acute leukemia, Pneumonia in ALL, Acute lymphoblastic leukemia

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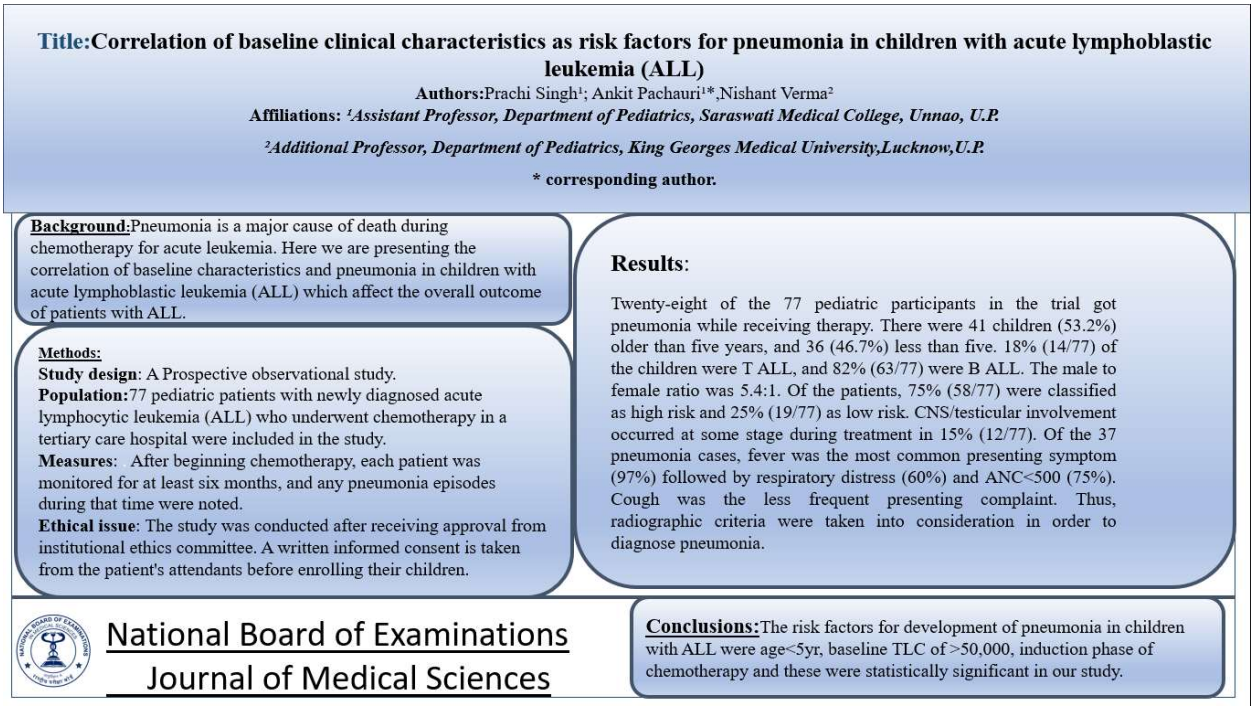
Graphical Abstract



Introduction

Acute leukaemia is a type of white blood cell cancer. Clinical symptoms of acute leukaemia are caused by the creation of aberrant (immature) white blood cells in greater quantities. Since these cells are aberrant, they don't guard against illnesses; instead, their proliferation reduces the creation of mature WBCs and other cell lines in the bone marrow's restricted space, which leads to anaemia, bleeding disorders, infections, and other problems. It is the most prevalent cancer among kids [1,2,3].

Children with impaired immune systems are more likely to experience respiratory tract infections, and their illness tends to progress more severely [4,5]. Despite significant improvements in chemotherapy treatments, leukaemia is one of the reasons of immunocompromised condition in children, which impacts the disease's cure rates. Therapy induced infection related complications in pediatric acute myeloid leukemia (AML) patients are well characterized [6-13]. However, there is limited data available on the prevalence, incidence, clinical features and outcome of pneumonia in children with acute lymphoblastic leukemia (ALL).

Burden of mortality due to respiratory infection is huge in children. Leowski estimated that acute respiratory infections caused 4 million child deaths each year [14]. Garenne et al. further refined these estimates by a study which revealed that between one-fifth and one-third of deaths in preschool children were due to or associated with acute respiratory infection [15].

Surviving ALL has significantly improved in developed nations, reaching 90%. The high incidence of acute infections, particularly pneumonias, continues to have a

detrimental effect on the prognosis of children receiving treatment for ALL in low- and middle-income nations like India [16-20].

High rates of severe infections are one factor contributing to these children's poor survival and morbidity in LMICs. Among these severe illnesses, pneumonias are the most frequent in children with ALL. Extended and intensified usage of chemotherapy medications is also linked to a higher risk of infection.

The purpose of this study is to estimate the relation of baseline characteristics with incidence of pneumonia in children with ALL.

Methods

Between January 2020 and March 2021, a total of 77 children with ALL who were admitted and received chemotherapy in the paediatric oncology unit division of the Department of Paediatrics, KGMU, Lucknow, were enrolled who met the inclusion criteria in this prospective cohort study. After beginning chemotherapy, each patient was monitored for at least six months, and any pneumonia episodes during that time were examined.

Approval from the Institutional Ethics Committee of the University Ref. code: 101 ECM II B- Thesis/P44 was taken and consent was taken from parents/relatives of enrolled patients.

Children (1-18yr) with a diagnosis of ALL on bone marrow morphology and flowcytometry were included in the study while children with pre-existing lung malformation, Children with mediastinal mass or with pleural effusion at the time of diagnosis of ALL were excluded. Newly diagnosed children with ALL admitted in pediatric oncology unit, meeting the inclusion and exclusion criteria and giving consent for participation in the study were prospectively enrolled. Their baseline characteristics were noted from their records and they were followed up prospectively till the end of study duration. Patients were managed according to standard treatment protocol under the guidance of the treating physician (3). If the child developed symptoms and signs (cough, fast breathing, retractions, cyanosis) suggestive of pneumonia during the study period, a Chest X ray was obtained to confirm the diagnosis of ‘Radiological Pneumonia’. The episode of pneumonia was managed as per the standard protocol. Outcome of each episode of pneumonia was recorded as cured or not cured. Standard definitions were used to define various conditions, for the purpose of this study ‘Pneumonia’ was referred only to children who had a radiologically confirmed pneumonia documented on a Chest X ray. Chest X ray was interpreted by two physicians independently (a pediatrician and a radiologist), and a child was labeled as ‘Pneumonia’ using the radiologically diagnosed pneumonia endpoints [21,22].

Data was recorded on standard case record form. Details of patients including age, sex, socioeconomic status, type, genetic forms, risk category, CNS involvement, initial TLC, and EOI (end of induction) MRD, phase of chemotherapy during which pneumonia episode occurred, radiological findings, clinical presentations of children with pneumonia, and outcome of ALL patients with pneumonia were recorded.

Statistical Analysis

Categorical variables were presented in number and percentage (%), and Odds ratios with 95% confidence intervals were calculated for selected variables as needed. Quantitative variables were compared using an unpaired t test between the two groups. Qualitative variables were compared using the chi-square or Fischer's exact test as appropriate. A p-value of <0.05 was considered statistically significant. The logistic regression analysis was done to find the independent factors associated with pneumonia in children with ALL. The data was entered in an MS Excel spreadsheet, and analysis was done using the Statistical Package for Social Sciences (SPSS) Version 24.0.

Results

Out of the 77 children receiving chemotherapy, there were 37 episodes of pneumonia among 28(36.4%) children who suffered from one or more episodes of pneumonia during the study period while, 49 (63.6%) children had no pneumonia episodes during the study period. 6(21.4%) children among the 28 affected by pneumonia 6 had >1 episodes, while rest 22(78.5%) suffered from a single episode of pneumonia. 36(46.7%) children aged <5 years while 41(53.2%) were >5yr of age. The male to female ratio was 5.4:1. 18% (14/77) children of T ALL and 82% (63/77) 63 of B ALL. 75% (58/77) patients were categorized as high risk while 25% (19/77) as low risk. 15% (12/77) had CNS/testicular involvement at some point during treatment.

Fever, either alone or in combination, was the most common presenting symptom in 36 (97.29%) of the pneumonia episodes. Cough was the presenting clinical characteristic in 23 (62.1%) of the incidents. In 22 cases of pneumonia (59.4%), the initial symptom was respiratory distress. In 28 cases of pneumonia, the absolute neutrophil count (ANC) was reduced (75.6%), whereas in 9 cases (24.3%), the ANC was normal.

Table 1. Distribution of clinical parameters in the 37 pneumonia episodes in children with ALL

Variable	**Category**	**No.**	**%**
Fever	No	1	2.7
	Yes	36	97.29
Respiratory Distress	No	23	62.1
	Yes	14	37.8
Cough	No	15	40.5
	Yes	22	59.4
ANC	<500	28	75.6

ANC- absolute neutrophile count; No. – number.

The majority of pneumonia occurrences occurred during the chemotherapy induction phase; that is, 22 incidents (59.4%) occurred during the induction phase, while 6 episodes (16.2%) occurred during the consolidation phase. Five (13.5%) of the pneumonia episodes were in the maintenance phase, three (8.1%) were during delayed intensification, and one (2.7%) occurred during interim maintenance.

Table 2. Distribution of occurrence of pneumonia episodes according to the phase of chemotherapy

Variable	**Category**	**No.**	**%**
Phase Of Chemo-therapy	**Induction**	22	59.4
	Consolidation	6	16.2
	Interim maintenance	1	2.7
	Delayed intensification	3	8.1
	Maintenance	5	13.5

The findings showed that children under the age of five had a 1.9-fold increased risk of contracting pneumonia, which was statistically significant. Males were 1.4 times more likely than females to get pneumonia, but there was no significant difference in the incidence of pneumonia between socioeconomic classes; that is, the incidence of pneumonia is about equal in both low and middle SES groups.

Table 3. Age, Gender and SES wise distribution of children suffering from pneumonia and their association

Variable		**Pneumonia**		P-value/R. R (CI)
		No	**Yes**	
		N **%**	N **%**	**0.04/1.9 (0-0.07)**
Age (Yrs)	**<5**	18 **52.8**	18 **47**	
	>5	30 **73.1**	11 **27**	
Sex	**F**	8 **72.7**	3 **27**	0.5/1.4 (0.5-3.8)
	M	41 **62.1**	25 **38**	
SES	**Low.**	44 **63.8**	25 **36**	0.9/0.9 (0.4-2.5)

	Mid.	5 **62.5**	3 **37**	

SES- socioeconomic status; Low. Lower SES; Mid.- Middle SES; F- female; M- Male; R.R- relative risk; C.I- confidence interval.

Pneumonia was more common in patients who presented with CNS/testicular involvement. The risk of pneumonia was calculated to be 1.5 times higher for patients in the high-risk group than for those in the standard-risk group. However, when significance tests were used, these results were not statistically significant.

Table 4. Correlation of CNS/Testicular involvement and risk group with pneumonia episodes in children with ALL

Variable		**Pneumonia**		**P-value/R. R**
		No	**Yes**	
		N **%**	N **%**	0.7/ 1.17
CNS/ Testicular +ve	**NO**	42 **65**	23 **35**	
	YES	7 **60**	5 **42**	0.3/ 1.5
Risk	**Std.**	14 **74**	5 **26**	
	High	35 **60**	23 **40**	

CNS/TESTICULAR +- CNS & testicular involvement present; Std.- standard risk; High- High risk; R.R – relative risk.

Our study found that children who presented with a baseline TLC of >50,000 had a quantitatively larger relative risk of developing pneumonia than their counterparts with a TLC of <50,000. This difference was also statistically significant. Although patients with EOI MRD+ had a higher quantitative incidence of pneumonia, statistical significance could not be confirmed when tests of significance were applied.

Table 5. Baseline Total leucocyte count and Minimal residual disease as risk factors for pneumonia

Variable		**Pneumonia**		**P-Value/ R. R**
		No	**Yes**	
		N **%**	N **%**	
TLC	**<50000**	37 **71**	15 **29**	**0.04/ 1.8**
	>50000	12 **48**	13 **52**	
EOI MRD	**Negative**	32 **68**	14 **32**	0.19/ 0.28
	Positive	11 **61**	6 **39**	

TLC-Total leucocyte count; EOI MRD- end of induction minimal residual disease; R.R- relative risk

Discussion

Immunocompromised children are more prone to develop respiratory tract infections and the disease course tends to be more severe in these children. One of the causes of immunocompromised status in children is leukemia, thus affecting the cure rates of the disease despite major advancements in chemotherapy regimens [1,2,3].

Pneumonia is the leading cause of de ath for children aged 1 to 59 months, with di arrhoea coming in second, illustrating the we ight of this illness [16,17,18].

Studies in various parts of the world show that on average, young children under 5 years of age suffer 4 to 6 episodes of acute respiratory infections per year and that one-third to a half of the outpatient pediatric consultations in developing countries are due to ARI. This count is higher in immunocompromised patients, like in leukaemia [16,17,18].

The diagnosis of pneumonia in leukemia can be difficult for many reasons: an impaired inflammatory response can reduce the clinical or radiological signs, therefore, here we chose radiological evidence to define a patient as having pneumonia [21,22]. Among these patients a higher incidence of pneumonia was seen in high-risk cases than the standard risk ones, which is due to higher doses and more intensive chemotherapy treatment plan followed in high-risk cases, which leads to a greater degree of myelosuppression in turn leading to higher incidence of pneumonia [6,7,8]. We also observed in our study that the maximum number of pneumonia episodes occurred during the induction phase of chemotherapy, i.e., 22 episodes (59.4%) out of the 37 episodes, as the induction phase

involves institution of more intensive chemotherapy than other phases therefore, higher myelosuppression occurs, which is why these children have lower absolute neutrophil counts. Therefore, these children have higher incidence of pneumonia in induction phase and over all higher incidence of fungal pneumonia due to immunocompromised state.

Our study looked at the following factors for a higher association with pneumonia: age (children aged >5 years vs. <5 years), gender (male and female), socioeconomic status, genetic translocations, baseline TLC (>50,000 or <50,000), CNS/testicular involvement, risk stratification, and MRD status at the end of induction.

Since there aren't many studies on pneumonia in pediatric acute leukaemia, we've attempted to compare a few pertinent studies here. In 2021, Mairuhu et al. came to the conclusion that risk stratification, chemotherapy phase, and neutropenia significantly influenced the incidence of hospital-acquired pneumonia in children with acute lymphoblastic leukaemia undergoing chemotherapy. This finding was fairly similar to our study, which found that higher incidence of pneumonia was observed in high-risk cases, chemotherapy induction phase, and lower neutrophil counts. However, because there were no two groups to compare, we were unable to ascertain the statistical significance of the association between pneumonia and induction phase and low ANC levels. Age, sex, nutritional condition, duration of hospitalisation, anaemia, and thrombocytopenia have not been found to be risk factors for hospital-acquired pneumonia in children [23].

According to Garracia et al., pneumonia was more common in people over 60, those with lower baseline platelet counts, low albumin levels, and neutropenia, but ALL was linked to a lower prevalence of pneumonia than AML.Since the adult population was the focus of this study, there is little correlation between it and ours [13]. Advanced age was found to be substantially correlated in another retrospective study by Specchia G et al.(24); however, since the study was carried out on adults, it is not very relevant to us.

Conclusion

The study demonstrates the risk factors which have been found to be associated with higher incidence, according to which an inference was made that pneumonia is a quite common complication in children with ALL with a higher incidence seen during induction phase of chemotherapy. We also concluded that age <5 yr and a baseline TLC>50,000 were significantly associated with increased risk of pneumonia.

Conflict of interest

The authors affirms that they do not have conflict of interest.

Funding

No financial help has been taken during the study.

Strengths of the study

1. There have been very few studies conducted on pneumonia in children with ALL. We have determined the risk factors

for pneumonia which in turn affect the outcome in children suffering from ALL.
2. Whenever a child developed symptoms and signs (cough, fast breathing, retractions, cyanosis) suggestive of pneumonia during the study period, a Chest X ray was obtained to confirm the diagnosis of 'Radiological Pneumonia. A robust clinico-radiological definition of Pneumonia was used.
3. We did a prospective observational study while most of the other studies were recorded retrospectively.
4. There was no loss to follow up.

Limitations of the study

1. The children admitted here mostly come from a lower socio-economic-strata, thus higher risk of acquiring infections due to poor hygiene. In our study population 89% patients were of low socio-economic-strata (SES) while none of the patients were from upper SES.
2. Most of the children come from distant places for treatment and the families being poor, prolong the hospital stay of the child as they do not want to stay outside due to affordability issue, thus increasing the duration of infection exposure.

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