

Study of Factors Affecting the Time to Diagnosis and Treatment in Pediatric Acute Leukemia Patients- A study from India

Abstract

Timely diagnosis and early initiation of treatment of acute leukemia in children improve survival. Our study aimed to identify the factors associated with delayed diagnosis of acute leukemia in children. A prospective observational study was done at a tertiary care Superspeciality hospital in Northern India. The study included 100 children aged 0–12 years over 18 months with the diagnosis of acute leukemia. A mixed-methods technique was used, combining important variables with qualitative interviews. The primary caregivers of each patient were asked to fill out a standardized questionnaire for this study in addition to the information recorded in the case record form, Demographic, clinical, and Healthcare system data were documented. Patient, physician, and health care system factors that cause delayed diagnosis were studied. Female sex (p-value = 0.003), the primary response to illness (p-value <0.001), lower socio-economic strata, and traveling Time to the nearest health care facility of more than 20–40 minutes were significant factors identified as the reason for the delay in acute leukemia diagnosis by more than eight weeks. There is a significant time lag between the onset of the first symptom and diagnosis of acute leukemia which may adversely affect the outcome. A concerted effort to improve the health care system and raise awareness of signs and symptoms of acute leukemia among caregivers and primary care physicians is required.

Keywords: Leukemia, Diagnosis, Delay, Treatment

Introduction

The improvement in the overall survival of pediatric acute leukemia is a great success story. Despite significant advances, it remains a leading cause of death amongst children in LMIC. Childhood leukemia is treatable as long as it is diagnosed and treated early.^[1,2] The total delay in diagnosis is the time interval from the onset of the first symptom to its final diagnosis.^[1] Brasme *et al.* reported a median delay of 2–260 weeks.^[3] Delay in diagnosing cancer may be broadly classified as patient-focused or healthcare provider-focused.^[4] Andersen *et al.*^[5] describe a "total patient delay" model and provide six stages of delayed symptom interpretation at the beginning of treatment. These are *appraisal* (lag in interpreting the symptoms); *illness* (delay in seeking medical attention); *appointment* (scheduling sluggishness is a behavioral trait), *scheduling* (the delay between appointment making and the first visit); and *treatment* (treatment postponement).

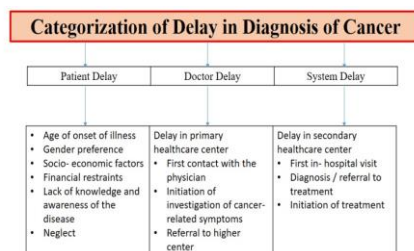
The major limitation of this model was that it mainly focused on patient delays and not

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on delays attributable to the health care system. Hansen *et al.*^[6] provided a model that described patient-related delays and physician-related delays in primary and secondary care. It classified the delays as patient delays, doctor delays, and system delays.

It has been graphically presented in **Figure 1**.



Modified from: Hansen RP *et al.* Socioeconomic patient characteristics predict delay in cancer diagnosis: A Danish cohort study. BMC Health Services Research 2008; 8: 49

Figure 1. Categorization of Delay in Diagnosis of Cancer

Symptom recognition, i.e., how the patient interprets their symptoms to influence their health-seeking behavior; caregivers who don't identify their child's symptoms as serious or related to cancer are more likely

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to delay seeking the HCS.^[7] Smith *et al.* identified fear of cancer and embarrassment as key factors that delay seeking healthcare facilities.^[8]

Doctor delay refers to the interval between the first hospital visit, the referral for diagnostic tests, and the specialist referral. In a systemic review by Mitchell *et al.*,^[9] misdiagnosis at the initial visit and preliminary examination by the physician were the two most common reasons for doctor's delays. System delay refers to the delay between the referral, final diagnosis, and the initiation of treatment and includes waiting Time for tests, non-urgent referrals, and administrative delays.

Survival rates are better in high-income countries (HIC) when compared with low and middle-income countries (LIC-MIC) like India (80% vs 10–30%).^[10] Reasons for the considerable survival gap are multifactorial. It has been seen that delay of 3–6 months is associated with lower survival.^[11] In India, delays are sometimes much longer than this, and some patients are never diagnosed at all.^[12] Non-specific symptoms in children, age of presentation, caregiver insight, knowledge and perception of illness, socioeconomic circumstances, accessibility to a health care center, affordability of treatment, healthcare worker (HCW) knowledge and awareness of the disease, belief in its curability and prompt referral to a hospital with a diagnostic and treatment facility are all factors that can contribute to a delayed diagnosis of childhood leukemia.^[13-15] Treatable leukemia becomes more challenging to treat or completely incurable. This can result in serious consequences, such as serious complications, deformations, and death. The chances of survival can be enhanced through early diagnosis and treatment.^[16] Recognition of the delays and factors influencing them is a major concern in pediatric cancer programs. This study aims to determine the factors that affect delay in diagnosis and initiation of treatment in pediatric patients with acute leukemia.

Materials and Methods

Study design

A prospective observational study.

Study setting

Super-specialty Hospital in New Delhi, India.

Study period

The study lasted 18 months, from July 1, 2018, to December 31, 2019.

Sample selection

Children with newly diagnosed leukemia, aged 0–12 years, who may or may not have commenced first-line treatment (curative or palliative intent, no more than one month before the date of recruitment) presenting to our center were enrolled. Non-malignant hematological conditions such as thalassemia, hemophilia, and pediatric cancers other than acute leukemia who presented with relapse were excluded. A convenient sample size of 100 patients was taken considering the study

period of 18 months and the 4-5 patients newly diagnosed with acute leukemia each month per the previous records. Patients were consecutively enrolled as they presented to the hospital. Descriptive statistics were used to describe categorical variables.

Ethical clearance was taken from the institute's ethical committee: IEC/VMMC/SJH/Thesis/October/2018/10

Data collection

A semi-structured quantitative questionnaire developed by the authors was completed by each patient's primary care provider and parents, enabling them to tell their story chronologically within a week of the final diagnosis. The interview was conducted with the informed consent of the treating physician, nurses, and support personnel. The attending doctor, nurse, and support staff were informed about the study before data collection. After taking informed consent from the primary caregiver or parents of the patient, key variables were noted in the case record form. Key variables included age and sex of the patient, the first symptom noted, educational classification and socioeconomic status of parents or caregivers as per the Modified Kuppaswamy scale (Appendix I), Time taken to reach the hospital and primary reaction to the sickness. The complete Case Report form (CRF) is included in appendix II.

Statics analysis

The presentation of the Categorical variables was done in the form of numbers and percentages (%). The association of the qualitative variables was analyzed using Fisher's exact test as at least one cell had an expected value of less than 5. The data entry was done in the Microsoft EXCEL spreadsheet, and the final analysis was done using Statistical Package for Social Sciences (SPSS) software, IBM manufacturer, Chicago, USA, ver 21.0. A p-value of less than 0.05 was considered statistically significant for statistical significance.

Results and Discussion

The patient's and disease characteristics are shown in **Table 1**. Most patients (n= 54; 54%) belonged to the age group 6-9 years, with a male predominance (68%).

Table 1. Distribution of demographic and baseline characteristics of study subjects.

Demographic and baseline characteristics	Frequency	Percentage
Age(years)		
3-6 years	41	41.00%
6-9 years	54	54.00%
9-12 years	5	5.00%
Gender		
Female	32	32.00%
Male	68	68.00%
Religion		
Hindu	73	73.00%
Muslim	27	27.00%
Chief complaints		
Bleeding	12	12.00%
Fever	64	64.00%

Others	22	22.00%
Petechiae	2	2.00%
Socioeconomic status		
Lower	72	72.00%
Middle lower	6	6.00%
Upper lower	22	22.00%
Annual family earning		
Up to 2000 Usd	42	42.00%
2000 - 3000 Usd	49	49.00%
3000 - 4000 Usd	1	1.00%
>4000 Usd	8	8.00%

Homeopathy treatment was taken by 32% (n=32) of patients themselves, and 22% (n=22) of patients ignored the symptoms. The Time taken for diagnosis since the onset of symptoms was more than eight weeks in the majority (76%) of patients. The distribution of taken for diagnosis since the beginning of symptoms and the association of the variables with Time taken for diagnosis since the onset of symptoms are shown in **Table 2**.

Table 2. Distribution of Time taken for diagnosis and association of characteristics with Time taken for diagnosis since the onset of symptoms of study subjects.

Characteristics	0-4 weeks (n=4) 4.00%	4-8 weeks (n=22) 22.00%	8-12 weeks (n=36) 36.00%	>12 weeks (n=38) 38.00%	Total (n=100) 100.00%	P value
Age(years)						
3-6 years	2 (4.88%)	8 (19.51%)	14 (34.15%)	17 (41.46%)	41 (100%)	0.987*
6-9 years	2 (3.70%)	13 (24.07%)	20 (37.04%)	19 (35.19%)	54 (100%)	
9-12 years	0 (0%)	1 (20%)	2 (40%)	2 (40%)	5 (100%)	
Gender						
Female	0 (0%)	2 (6.25%)	10 (31.25%)	20 (62.50%)	32 (100%)	0.001*
Male	4 (5.88%)	20 (29.41%)	26 (38.24%)	18 (26.47%)	68 (100%)	
Primary reaction to sickness						
Allopathy	2 (4.35%)	13 (28.26%)	15 (32.61%)	16 (34.78%)	46 (100%)	0.208*
Homeopathy	2 (6.25%)	4 (12.50%)	16 (50%)	10 (31.25%)	32 (100%)	
Ignored	0 (0%)	5 (22.73%)	5 (22.73%)	12 (54.55%)	22 (100%)	
Time taken to reach health care						
0-20 minutes	3 (6.25%)	10 (20.83%)	16 (33.33%)	19 (39.58%)	48 (100%)	0.624*
20-40 minutes	1 (2%)	12 (24%)	20 (40%)	17 (34%)	50 (100%)	
40-60 minutes	0 (0%)	0 (0%)	0 (0%)	2 (100%)	2 (100%)	
Socioeconomic status						
Lower	3 (4.17%)	16 (22.22%)	28 (38.89%)	25 (34.72%)	72 (100%)	0.775*
Middle lower	0 (0%)	1 (16.67%)	3 (50%)	2 (33.33%)	6 (100%)	
Upper lower	1 (4.55%)	5 (22.73%)	5 (22.73%)	11 (50%)	22 (100%)	
Annual family earning						
Up to 2000 Usd	0 (0%)	9 (21.43%)	13 (30.95%)	20 (47.62%)	42 (100%)	0.113*
2000 - 3000 Usd	3 (6.12%)	12 (24.49%)	18 (36.73%)	16 (32.65%)	49 (100%)	
3000 - 4000 Usd	0 (0%)	1 (100%)	0 (0%)	0 (0%)	1 (100%)	
>4000 Usd	1 (12.50%)	0 (0%)	5 (62.50%)	2 (25%)	8 (100%)	

Twenty-six out of thirty-three patients (81.25%) who sought homeopathy as an initial treatment suffered a delayed diagnosis of more than eight weeks. Out of 72 patients belonging to the lower class, 53 patients were diagnosed after eight weeks. Similarly, 33 out of 42 families with an annual income of less than 2000 USD suffered a delayed diagnosis of more than eight weeks.

The main challenge faced by the caregivers while seeking treatment was guidance regarding when and how to seek the healthcare facilities (93%), followed by a lack of money to travel to Healthcare centers and seek medical attention (68%).

Patient delay was seen in all patients, followed by doctor delay (31(31.00%)). System delay occurred in only 16 out of 100 patients (16.00%). It has been shown in **Table 3**.

Table 3. Distribution of delay of study subjects.

Delay	Frequency	Percentage
Patient delay	100	100.00%
Doctor delay	31	31.00%
System delay	16	16.00%

The association of patient characteristics with a delay has been shown in **Table 4**.

Table 4. Association of characteristics with delay.

Characteristics	Only patient delay(n=69)	Patient and doctor delay(n=15)	Patient, doctor and system delay(n=16)	Total	P value
Age(years)					
3-6 years	25 (60.98%)	7 (17.07%)	9 (21.95%)	41 (100%)	0.409*
6-9 years	41 (75.93%)	7 (12.96%)	6 (11.11%)	54 (100%)	
9-12 years	3 (60%)	1 (20%)	1 (20%)	5 (100%)	
Gender					
Female	21 (65.63%)	1 (3.13%)	10 (31.25%)	32 (100%)	0.003*
Male	48 (70.59%)	14 (20.59%)	6 (8.82%)	68 (100%)	
Primary reaction to sickness					
Allopathy	15 (32.61%)	15 (32.61%)	16 (34.78%)	46 (100%)	<.0001*
Homeopathy	32 (100%)	0 (0%)	0 (0%)	32 (100%)	
Ignored	22 (100%)	0 (0%)	0 (0%)	22 (100%)	
Time taken to reach health care					
0-20 minutes	30 (62.50%)	8 (16.67%)	10 (20.83%)	48 (100%)	0.683*
20-40 minutes	37 (74%)	7 (14%)	6 (12%)	50 (100%)	
40-60 minutes	2 (100%)	0 (0%)	0 (0%)	2 (100%)	
Socioeconomic status					
Lower	53 (73.61%)	9 (12.50%)	10 (13.89%)	72 (100%)	0.337*
Middle lower	3 (50%)	1 (16.67%)	2 (33.33%)	6 (100%)	
Upper lower	13 (59.09%)	5 (22.73%)	4 (18.18%)	22 (100%)	
Time taken for diagnosis since the onset of symptoms					
0-4 weeks	2 (50%)	2 (50%)	0 (0%)	4 (100%)	<.0001*
4-8 weeks	9 (40.91%)	13 (59.09%)	0 (0%)	22 (100%)	
8-12 weeks	36 (100%)	0 (0%)	0 (0%)	36 (100%)	
>12 weeks	22 (57.89%)	0 (0%)	16 (42.11%)	38 (100%)	
Annual family earning					
Up to 2000 Usd	32 (76.19%)	3 (7.14%)	7 (16.67%)	42 (100%)	0.097*
2000 - 3000 Usd	31 (63.27%)	11 (22.45%)	7 (14.29%)	49 (100%)	
3000 - 4000 Usd	0 (0%)	1 (100%)	0 (0%)	1 (100%)	
>4000 Usd	6 (75%)	0 (0%)	2 (25%)	8 (100%)	

* Fisher's exact test

Gender, primary reaction to illness, and Time to diagnosis since the onset of symptoms are significantly associated with the delay ($p < 0.05$).

The study found a significantly higher proportion of females (21 out of 32 females) being diagnosed after eight weeks of the onset of symptoms compared to male patients (p -value < 0.001). A significantly higher proportion of Patients in the Lower economic class were diagnosed after more than 12 weeks compared to patients in the Lower middle class & Upper Lower Class (p -value 0.016), as per the modified Kuppusswamy scale.

There was a significant correlation between chief complaints and the Time taken for diagnosis since the onset of symptoms. Patients with bleeding had early diagnosis compared with

patients with body aches, fever, and pallor (p -value 0.038). There was a significant correlation between the patient's take to reach the healthcare facility and the Time taken for diagnosis since the onset of symptoms (p -value 0.043).

Financial problems (money for outpatient department visits, inpatient expenses on treatment, investigations, treatment, and travel expenses) were significant for patients with delayed diagnoses (p -value 0.019).

Our study aims to find the factors responsible for the delay in diagnosis of pediatric ALL. Numerous pieces of literature regarding the same have been published from developed countries, but there is a lack of data concerning this problem from the developing nations, e.g., India. A thorough understanding of the factors responsible for this delay is

necessary so that measures can be taken to reduce and avoid them and improve survival. Our study found that the taken to diagnose leukemia is affected by socioeconomic status, gender, Time taken to reach the health care facility, patient compliance, referral system (delayed referral from primary and secondary HCS to tertiary HCS), and ignorance of mild symptoms. Out of these, gender bias (female child), low socioeconomic status, patient compliance, nature of presenting complaint, primary reaction to sickness (acceptance vs denial, first treatment sought), and Time taken to reach health care facility. Financial problems (money for OPD visits, inpatient expenses on treatment, investigations, treatment, and travel expenses) were significant, with a p-value of < 0.05. The average delay in the diagnosis of acute leukemia was around eight weeks, which caused late initiation of treatment of the patients. Similar results were derived by Venkatasai JP *et al.*^[17] To minimize this delay, adequate parenteral education and support are needed. Creating a mass awareness regarding the symptomatology and nature of the disease via campaigns, television and radio broadcast, and the internet is necessary. Our study noticed late health-seeking behavior for the mild symptoms in the female child compared to the male child, which led to a delay in diagnosis. There was a male preponderance of cases possibly due to selective health-seeking behavior.^[18] Gender bias in seeking healthcare facilities accounts for an important social problem that exists in LIC-MIC, e.g. in India.^[19, 20]

In our study, financial problems were significant in causing this delay. 75.4% showed a delay in diagnosis of more than 12 weeks. Providing financial aid for medical and non-medical expenses might prevent the delay.

A systemic review of observational studies (worldwide) conducted by Richards *et al.* showed that delays of 3–6 months were associated with lower survival.^[21] In LMIC, these delays can be much longer because of lack of awareness, illiteracy, longer waiting time, disproportionate doctor-patient ratio, and lack of good healthcare facilities in peripheries and tribal areas. Many times some patients are never diagnosed at all; as seen in our study, patients had to face a delay of more than 12 weeks due to various demographic factors.^[22]

A study conducted in Egypt by ER Abdelkhalek *et al.*^[23] observed that a child's sex, age at diagnosis, type and site of malignancy, family residence, socioeconomic status, and parental educational level played a significant role in causing this delay, and the median total diagnosis delay period was 47 days. Mamtaz Begum *et al.*^[24] found that 70% of the cases had to wait for more than 90 days for treatment in Bangladesh. In our study, 76% of the children had to face a delay of more than eight weeks in getting a proper diagnosis and treatment.

Patients' delay in our study occurred due to the age at which the disease was presented, the family's financial background, and the parents' education status. Raising awareness among the stakeholders can minimize this problem.

Indian population has its varied reasons for the increased time interval from symptom onset to diagnosis and treatment. Social beliefs, poverty, lack of easy access to health care, girl child, illiteracy, and beliefs in traditional alternative medicines are a few of the factors responsible for the late presentation of Indian children with cancer.^[25]

Leukemia remains a leading cause of death in children despite the tremendous advancement in pediatric oncology during the past two decades.^[26] Early diagnosis is the fundamental key to leukemia management because it can allow early treatment of the disease, resulting in a better prognosis and positively affecting their quality of life.^[27, 28]

Research on diagnosis delays in childhood leukemia is still in its early stages. More studies are needed to investigate the potential impact of delays on prognosis outcomes. The Time taken to diagnose acute leukemia in India is around three months. Female children, lower economic strata, financial problems, and delay in reaching healthcare facilities were some of the significant factors which resulted in a delayed diagnosis of more than three months.

Conclusion

Early diagnosis is recommended to improve the survival rate of children with leukemia. Raising public awareness of the disease will play a vital role in reducing the delay in diagnosis and is a must to identify danger signs, which otherwise are easily ignored by most parents. Counseling the parents and the caregivers regarding the nature of the disease, its symptomatology, nature of the treatment, and durability, and providing adequate and appropriate social support through public support groups can help in the early identification of the symptoms and early seeking of treatment.^[29] There is a need for more quantitative studies with a larger sample size to consolidate our understanding of various factors affecting the outcome of pediatric cancer patients.

Limitations

Our single-centered study with a smaller sample size may not represent the entire population's characteristics. Our study did not take into account delays associated with non-hematological malignancy. Additionally, recall bias due to the chronicity of the disease can be a major confounder in our findings.

Disclaimer

The views expressed in the submitted article are their own and not an official position of the institution or funder.

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Conflict of interest

None.

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None.

Ethics statement

IEC/VMMC/SJH/Thesis/October/2018/10 (ethical approval obtained from ethical committee of Vardhman Mahavir Medical College and Safdarjung Hospital, Guru Gobind Singh Indraprastha University, New Delhi, India).

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