Society of Medical Education & Research

2022, Volume 2, Issue 2, Page No: 37-44
Copyright CC BY-NC-SA 4.0

Archive of International Journal of Cancer and Allied Science

Factors Influencing Time to Diagnosis and Treatment in Pediatric Acute Leukemia: Insights from an Indian Cohort

Gaurav Singh[1], Neha Goel[1], Amitabh Singh[1], Rani Gera[1*]

[1] Department of Pediatrics, VMMC & Safdarjung Hospital, New Delhi, India.

***E-mail** ✉ drranigera@gmail.com

Abstract

Early diagnosis and prompt treatment of pediatric acute leukemia are crucial for improving survival outcomes. This study aimed to investigate the factors contributing to delays in diagnosing acute leukemia in children. A prospective observational study was conducted at a specialized hospital in Northern India, enrolling 100 children aged 0-12 years over 18 months. A combination of quantitative data and qualitative interviews was used to gather insights. Caregivers completed a standardized questionnaire alongside case record data, documenting demographic, clinical, and healthcare system-related factors. Our analysis identified several key contributors to delayed diagnosis, including female gender (P-value = 0.003), initial health responses (P-value < 0.001), lower socioeconomic status, and travel times of over 20–40 minutes to healthcare facilities. These factors were associated with diagnostic delays exceeding eight weeks. The delay between symptom onset and diagnosis was significant and may negatively impact patient outcomes. This highlights the need for targeted efforts to improve healthcare infrastructure and increase awareness of leukemia symptoms among caregivers and healthcare providers.

Keywords: Pediatric Leukemia, Diagnostic Delay, Treatment, Healthcare System

Introduction

The significant improvement in the survival rates of pediatric acute leukemia marks a major medical achievement. However, despite these advances, leukemia remains one of the top causes of childhood mortality, particularly in low- and middle-income countries (LMIC). Early diagnosis and timely treatment are key to effectively managing childhood leukemia [1, 2]. The total diagnostic delay is defined as the period between the first appearance of symptoms and the final diagnosis [1]. Brasme *et al.* [3] identified a wide range of delays, with a median delay from 2 to 260 weeks [3]. Delays in cancer diagnosis can be categorized into two main types: those attributed to the patient and those due to healthcare providers [4]. Andersen *et al.* [5] proposed a "total patient delay" model, which outlines six stages that contribute to the delay in diagnosis: appraisal (difficulty in recognizing symptoms), illness (hesitation in seeking medical help), appointment (slow response in scheduling), scheduling (the wait between booking and the initial visit), and treatment (delays in starting treatment).

One limitation of this model is its emphasis on patient delays, without accounting for those caused by the healthcare system itself. To address this, Hansen *et al.* [6] presented a more comprehensive model, distinguishing between delays caused by patients, physicians, and the healthcare system. This framework is illustrated in **Figure 1**.

Access this article online

Website: https://smerpub.com/ **E-ISSN: 3108-4834**

Received: 06 September 2022; **Revised:** 28 November 2022; **Accepted:** 06 December 2022

How to cite this article: Singh G, Goel N, Singh A, Gera R. Factors Influencing Time to Diagnosis and Treatment in Pediatric Acute Leukemia: Insights from an Indian Cohort. Arch Int J Cancer Allied Sci. 2022;2(2):37-44. https://doi.org/10.51847/FWfHO4xMyB

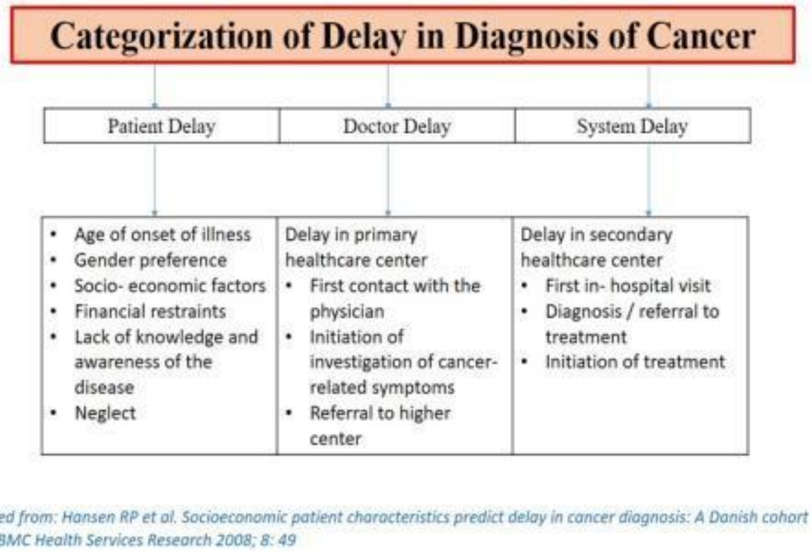

Figure 1. Categorization of delay in diagnosis of cancer

Symptom recognition is a crucial factor in health-seeking behavior. Caregivers who do not perceive their child's symptoms as severe or related to cancer tend to delay seeking medical care. Fear of cancer and embarrassment have been identified as significant barriers to prompt healthcare-seeking, further delaying diagnosis and treatment [7, 8].

Doctor delays occur between the patient's initial visit to the hospital, the referral for diagnostic tests, and the subsequent specialist referral. A systematic review by Mitchell *et al.* [9] revealed that misdiagnosis during the initial consultation and inadequate preliminary examination by the physician were the leading causes of delays in care. System delays, on the other hand, refer to the time lag between referral, diagnosis, and treatment initiation. This category includes waiting times for tests, non-urgent referrals, and administrative bottlenecks.

Survival outcomes are generally more favorable in high-income countries (HICs), where the survival rate is about 80%, compared to lower-income countries (LICs), such as India, where survival rates range from 10% to 30% [10]. The survival gap is influenced by several factors. Research has shown that delays of 3 to 6 months are associated with a lower survival rate [11]. In India, delays often exceed this range, and some patients may never receive a diagnosis [12]. Factors contributing to delays include non-specific symptoms in children, the age of presentation, caregiver awareness, socioeconomic status, access to healthcare facilities, affordability of treatment, healthcare worker knowledge, and the belief in the curability of the disease. Furthermore, timely referrals to hospitals equipped for diagnosis and treatment are critical in preventing delays [13-15].

Delays in diagnosing leukemia often make what is otherwise a treatable disease more difficult to manage, or even incurable, leading to severe complications, deformities, and death. Early diagnosis and treatment significantly improve survival rates [16]. Addressing these delays and understanding the factors that influence them are essential components of pediatric cancer care programs. This study seeks to identify the factors that contribute to delays in diagnosis and treatment initiation in children with acute leukemia.

Materials and Methods

Study design

This was a prospective observational study aimed at investigating the factors that contribute to delays in the diagnosis and treatment of pediatric acute leukemia.

Study location

The study was carried out at a super-specialty medical center in New Delhi, India, which provides advanced healthcare services.

Study period

The research was conducted over 18 months, starting from July 1, 2018, and concluding on December 31, 2019.

Participant criteria

The study enrolled children between the ages of 0 and 12 who had been recently diagnosed with acute leukemia. The inclusion criteria required that these children had either started their first-line treatment (whether curative or palliative) or had been diagnosed within one month of recruitment. Children with other hematological disorders, such as thalassemia or hemophilia, as well as those with recurrent leukemia, were excluded. Based on the hospital's historical data, a total of 100 children were recruited, which corresponded to an average of 4–5 new leukemia cases per month during the study period. Patients were included in the study as they arrived at the hospital. Categorical data were analyzed using descriptive statistics.

Ethics approval

The study received ethical approval from the Institutional Ethics Committee, with reference number IEC/VMMC/SJH/Thesis/October/2018/10.

Data collection method

Data were collected using a structured questionnaire, which was administered to the primary caregivers or parents of the children involved in the study. This questionnaire allowed the caregivers to recount their child's symptom history in a detailed, chronological manner within one week of diagnosis. The study was carried out with the full consent of the caregivers and approval from the treating medical staff. All healthcare professionals involved in the study were informed in advance. Following informed consent, various data points were recorded, including the patient's age and sex, initial symptoms, caregiver education level, socioeconomic status (based on the Modified Kuppuswamy Scale), travel time to the healthcare facility, and initial responses to the child's illness. The complete case report form (CRF) is available in Appendix II.

Statistical analysis

Data on categorical variables were expressed as frequencies and percentages. Fisher's exact test was applied to assess the relationships between categorical variables, due to the presence of small expected cell values. Data entry was done in Microsoft Excel, and statistical analyses were conducted using SPSS software (Version 21.0, IBM Corp., Chicago, USA). A P-value of less than 0.05 was considered to indicate statistical significance.

Results and Discussion

Table 1 highlights the demographic and baseline characteristics of the study participants. The majority (54%) of the patients were in the 6-9 year age group, with males comprising 68% of the sample.

Table 1. Demographic and baseline characteristics of study participants

Characteristic	Frequency	Percentage
Age (years)		
3-6	41	41.00%
6-9	54	54.00%
9-12	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 income (USD)		
Up to 2000	42	42.00%

2000-3000	49	49.00%
3000-4000	1	1.00%
> 4000	8	8.00%

A total of 32% of the patients (n = 32) opted for homeopathic treatments, while 22% (n = 22) did not seek any treatment for their symptoms. The majority of patients (76%) experienced delays in diagnosis of more than eight weeks following the onset of symptoms. **Table 2** presents the distribution of diagnosis times and the factors influencing the duration between symptom onset and diagnosis.

Table 2. Diagnosis time distribution and its association with various factors

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

Among the thirty-three patients who initially opted for homeopathy, 26 (81.25%) experienced a delayed diagnosis of over eight weeks. Similarly, 53 out of 72 patients from the lower socioeconomic group faced delays exceeding eight weeks in diagnosis. Additionally, 33 of the 42 families with an annual income of less than 2000 USD encountered a diagnosis delay of more than eight weeks.

The primary challenge caregivers faced while seeking medical care was unclear guidance on when and how to approach healthcare facilities (93%). This was followed by financial constraints preventing travel to healthcare centers and seeking necessary medical attention (68%).

Delays were observed in all patients, with the largest delay occurring due to patient factors, followed by doctor-related delays (31%). System-related delays were seen in only 16 out of 100 patients (16%). The detailed distribution of delays is shown in **Table 3**.

Table 3. Distribution of delay among study participants

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

The relationship between participant characteristics and the delay types is shown in **Table 4**.

Table 4. Association between characteristics and delays

Characteristic	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	25 (60.98%)	7 (17.07%)	9 (21.95%)	41	0.409*
6-9	41 (75.93%)	7 (12.96%)	6 (11.11%)	54	
9-12	3 (60%)	1 (20%)	1 (20%)	5	
Gender					0.003*
Female	21 (65.63%)	1 (3.13%)	10 (31.25%)	32	
Male	48 (70.59%)	14 (20.59%)	6 (8.82%)	68	
Primary response to illness					< 0.0001*
Allopathy	15 (32.61%)	15 (32.61%)	16 (34.78%)	46	
Homeopathy	32 (100%)	0 (0%)	0 (0%)	32	
Ignored	22 (100%)	0 (0%)	0 (0%)	22	
Time taken to reach healthcare (minutes)					0.683*
0-20	30 (62.50%)	8 (16.67%)	10 (20.83%)	48	
20-40	37 (74%)	7 (14%)	6 (12%)	50	
40-60	2 (100%)	0 (0%)	0 (0%)	2	
Socioeconomic status					0.337*
Lower	53 (73.61%)	9 (12.50%)	10 (13.89%)	72	
Middle lower	3 (50%)	1 (16.67%)	2 (33.33%)	6	
Upper lower	13 (59.09%)	5 (22.73%)	4 (18.18%)	22	
Time taken for diagnosis since onset (weeks)					< 0.0001*
0-4	2 (50%)	2 (50%)	0 (0%)	4	
4-8	9 (40.91%)	13 (59.09%)	0 (0%)	22	
8-12	36 (100%)	0 (0%)	0 (0%)	36	
> 12	22 (57.89%)	0 (0%)	16 (42.11%)	38	
Annual family income (USD)					0.097*
Up to 2000	32 (76.19%)	3 (7.14%)	7 (16.67%)	42	
2000 - 3000	31 (63.27%)	11 (22.45%)	7 (14.29%)	49	
3000 - 4000	0 (0%)	1 (100%)	0 (0%)	1	
> 4000	6 (75%)	0 (0%)	2 (25%)	8	

*Fisher's exact test

Gender, primary reaction to illness, and time to diagnosis impact delays significantly

The study highlighted significant associations between gender, the initial response to illness, and the time taken for diagnosis since symptom onset with delays (P < 0.05). A notably higher proportion of females (21 out of 32) experienced delays of over eight weeks in diagnosis compared to males (P-value < 0.001). Additionally, patients from lower socioeconomic backgrounds had longer delays, particularly those diagnosed after 12 weeks, in comparison to those from lower-middle and upper-lower classes (P-value = 0.016), as determined by the modified Kuppuswamy scale.

A significant link was found between the primary complaints and the time taken for diagnosis. Patients presenting with bleeding symptoms were diagnosed earlier than those with body aches, fever, or pallor (P-value = 0.038). Moreover, the time taken to reach healthcare facilities was significantly associated with the diagnosis time (P-value = 0.043).

Financial issues, including costs for outpatient visits, inpatient treatment, tests, and travel expenses, were significant contributors to delayed diagnoses (P-value = 0.019).

Study objective and findings

Our study aimed to identify the factors causing diagnostic delays in pediatric acute lymphoblastic leukemia (ALL). While similar studies have been conducted in developed countries, there is limited data on this issue from developing nations like India. Understanding these delays is crucial for implementing measures to reduce them and improve patient outcomes. The study identified several factors influencing diagnostic delays, including socioeconomic status, gender, the time it took to reach healthcare facilities, patient compliance, referral delays (from primary to tertiary healthcare centers), and the underestimation of mild symptoms.

Key contributing factors included gender bias (especially for female children), low socioeconomic status, patient compliance, the nature of the presenting complaints, the initial response to illness (whether they sought immediate care or denied symptoms), and the time taken to access healthcare. Financial constraints (covering outpatient visits, inpatient treatment, tests, and travel) were also major contributors to delayed diagnosis (P-value < 0.05).

Impact of delay on treatment

The average delay in diagnosing acute leukemia was approximately eight weeks, resulting in delayed treatment initiation. Similar findings were reported by Venkatasai *et al.* [17], to reduce this delay, enhanced education and support are necessary. Public awareness campaigns about the disease's symptoms, through television, radio, and the internet, are essential. Our study observed a delayed health-seeking behavior in female children compared to males, contributing to diagnostic delays. There was also a notable male predominance in cases, potentially due to gender-based health-seeking behavior differences. Gender bias in healthcare access is a significant issue in low- and middle-income countries (LMICs), such as India [18-20].

Financial constraints as a major cause of delay

In our study, financial issues were identified as a significant cause of diagnostic delay, with 75.4% of patients experiencing delays of over 12 weeks. Providing financial aid for medical and non-medical expenses could potentially reduce these delays.

Global context and previous studies

A systematic review by Richards *et al.* [11] on delays in diagnosis found that delays of 3–6 months were linked to lower survival rates. In LMICs, these delays may be even longer due to factors such as lack of awareness, illiteracy, long wait times, disproportionate doctor-patient ratios, and limited access to healthcare in peripheral or rural areas [11, 12]. In some cases, patients may never receive a diagnosis at all, as seen in our study, where delays exceeded 12 weeks due to demographic factors.

A study by Abdelkhalek *et al.* [21] in Egypt found that factors like the child's sex, age, type and location of the malignancy, socioeconomic status, and parental education level significantly contributed to diagnostic delays, with a median delay of 47 days. Begum *et al.* [22] in Bangladesh found that 70% of cases faced a delay of over 90 days in receiving treatment. In our study, 76% of children experienced delays of over eight weeks in diagnosis and treatment.

Factors contributing to delays in India

Our study found that delays in diagnosis were primarily due to the patient's age, family financial status, and parent's education level. Raising awareness among stakeholders, including parents and healthcare workers, could help reduce these delays. In India, factors such as social beliefs, poverty, lack of access to healthcare, gender bias, illiteracy, and reliance on traditional medicines contribute to the delayed presentation of children with cancer [1, 23-25].

Leukemia and the need for early diagnosis

Leukemia remains one of the leading causes of death among children despite significant advancements in pediatric oncology. Early diagnosis is crucial for effective treatment, which can improve prognosis and quality of life.

Research into diagnostic delays in childhood leukemia is still in its early stages, and more studies are needed to examine how delays impact prognosis. In India, the average time taken to diagnose acute leukemia is about three months. Significant factors contributing to this delay include gender (especially female children), low socioeconomic status, financial constraints, and delays in reaching healthcare facilities. Early interventions to address these factors could improve outcomes for pediatric leukemia patients [1, 24-26].

Limitations

This study's findings may not fully reflect the wider population due to its single-center approach and relatively small sample size. Additionally, we did not explore delays in diagnosing non-hematological cancers. The potential for recall bias, stemming from the long-term nature of the disease, may also have influenced our results.

Conclusion

For improving the survival chances of children with leukemia, timely diagnosis is critical. Increasing awareness about the disease among the public is crucial in shortening diagnostic delays. Many early symptoms are often ignored by parents, so educating them about these signs can help in early detection. Providing guidance and support to parents and caregivers about the disease, treatment options, and possible long-term effects, along with connecting them to public support networks, can significantly improve early diagnosis and treatment. Future studies with larger sample sizes are needed to further explore the factors that affect the outcomes of pediatric cancer patients.

Acknowledgments: None

Conflict of Interest: None

Financial Support: None

Ethics Statement: None

References

1. Dang-Tan T, Franco EL. Diagnosis delays in childhood cancer: a review. Cancer. 2007;110(4):703-13.
2. Stefan DC, Siemonsma F. Delay, and causes of delay in the diagnosis of childhood cancer in Africa. Pediatr Blood Cancer. 2011;56(1):80-5.
3. Brasme JF, Morfouace M, Grill J, Martinot A, Amalberti R, Bons- Letouzey C, et al. Delays in diagnosis of pediatric leukemias: a systematic review and comparison with expert testimony in lawsuits. Lancet Oncol. 2012;13(10):445-59.
4. Arndt V, Stürmer T, Stegmaier C, Ziegler H, Dhom G, Brenner H. Patient delay and stage of diagnosis among breast cancer patients in Germany–a population based study. Br J Cancer. 2002;86(7):1034-40.
5. Andersen BL, Cacioppo JT, Roberts DC. Delay in seeking a cancer diagnosis: delay stages and psychophysiological comparison processes. Br J Soc Psychol. 1995;34(1):33-52.
6. Hansen RP, Olesen F, Sørensen HT, Sokolowski I, Søndergaard J. Socioeconomic patient characteristics predict delay in cancer diagnosis: a Danish cohort study. BMC Health Serv Res. 2008;8(1):1-0.
7. Burgess C, Hunter MS, Ramirez AJ. A qualitative study of delay among women reporting symptoms of breast cancer. Br J Gen Pract. 2001;51(473):967-71.
8. Smith LK, Pope C, Botha JL. Patients' help-seeking experiences and delay in cancer presentation: a qualitative synthesis. Lancet. 2005;366(9488):825-31.
9. Mitchell E, Macdonald S, Campbell NC, Weller D, Macleod U. Influences on pre-hospital delay in the diagnosis of colorectal cancer: a systematic review. Br J Cancer. 2008;98(1):60-70.
10. Ellison LF, Pogany L, Mery LS. Childhood and adolescent cancer survival: a period analysis of data from the Canadian Cancer Registry. Eur J Cancer. 2007;43(13):1967-75.
11. Richards MA, Westcombe AM, Love SB, Littlejohns P, Ramirez AJ. Influence of delay on survival in patients with breast cancer: a systematic review. Lancet. 1999;353(9159):1119-26.
12. Arora B, Kanwar V. Childhood leukemias in India: burden, barriers, and breakthroughs. Indian J Cancer. 2009;46(4):257-9.
13. Arora RS, Eden T, Pizer B. The problem of treatment abandonment in children from developing countries with cancer. Pediatr Blood Cancer. 2007;49(7):941-6.
14. Mostert S, Gunawan S, Van Dongen JA, van de Ven PM, Sitaresmi MN, Wolters EE, et al. Health-care providers' perspectives on childhood cancer treatment in Manado, Indonesia. Psychooncology. 2013;22(11):2522-8.
15. Andersen RS, Paarup B, Vedsted P, Bro F, Søendergaard J.' Containment' as an analytical framework for understanding patient delay: a qualitative study of cancer patients' symptom interpretation processes. Soc Sci Med. 2010;71(2):378-85.
16. Brown BJ, Ajayi SO, Ogun OA, Oladokun RE. Factors influencing Time to diagnosis of childhood cancer in Ibadan, Nigeria. Afr Health Sci. 2009;9(4):247-53.
17. Venkatasai JP, Srinivasamaharaj S, Sneha LM, Scott JX, Baby AK, Rajan M. Pediatric hematological malignancy: Identification of issues involved in the road to diagnosis. South Asian J Cancer. 2017;6(1):28-30.
18. Kulkarni KP, Marwaha RK. The significant male preponderance in childhood acute lymphoblastic leukemia in India and regional variation: tertiary care center experience, systematic review, and evaluation of population-based data. Pediatr Hematol Oncol. 2013;30(6):557-67.

19. Arora RS, Eden TO, Kapoor G. Epidemiology of childhood cancer in India. Indian J Cancer. 2009;46(4):264-73.
20. Verma N, Bhattacharya S. Time to diagnosis and treatment of childhood cancer. Indian J Pediatr. 2020;87(8):641-3.
21. Abdelkhalek ER, Sherief LM, Kamal NM, Soliman RM. Factors Associated with Delayed Cancer Diagnosis in Egyptian Children. Clin Med Insights Pediatr. 2014;8:39-44.
22. Begum M, Islam MJ, Akhtar MW, Karim S. Evaluation of delays in diagnosis and treatment of childhood malignancies in Bangladesh. South Asian J Cancer. 2016;5(4):192-3.
23. Ramzan M, Yadav SP, Sachdeva A. Treatment abandonment is a major hurdle for improving survival in childhood cancer in the developing world. Pediatr Blood Cancer. 2013;60(1):159-60.
24. Reaman GH. A national approach to evaluating delays in diagnosis and treatment: potential implications for age-related and geo-political differences in access to care and outcome in children and adolescents with cancer. Pediatr Blood Cancer. 2008;51(4):447-8.
25. Klein-Geltink JE, Pogany LM, Barr RD, Greenberg ML, Mery LS. Waiting times for cancer care in Canadian children. Impact of distance, clinical and demographic factors. Pediatr Blood Cancer. 2005;44(4):318-27.
26. Nair M, Parukkutty K, Kommadath S. Effect of a new social support program by voluntary organization in the pediatric oncology department in a developing country. Pediatr Hematol Oncol. 2014;31(3):212-6.