



A Retrospective Study of Factors Affecting Pathway and Time to Diagnosis, Time to Treatment in Children with Cancer in a Single Center in South India

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Abstract

Introduction The overall cure rate of childhood cancers is above 79% in the developed world, whereas in the developing world, like in India, it is around 50%. It is vital to know the routes of presentation and factors affecting the presentation of childhood cancers in primary, secondary, and tertiary care to design a better survival strategy in childhood cancer.

Objective The aim of this study was to know the factors affecting the time to diagnosis and time to treatment in children with cancers in a single center in South India.

Materials and Methods It was a retrospective cohort study of children diagnosed with cancer between January 1, 2014 and December 31, 2016 at the pediatric oncology unit, KMC Hospital Mangalore, India. The patient interval, time to diagnosis, patient's family, economic background, parental education, and referral pattern were recorded, and its impact on the time taken to diagnosis was studied. The data was analyzed using SPSS 20.0 software.

Results Out of 111 children, 72 were boys (64.8%). Fifty-one (46%) children belonged to the less than 5-year age group. The most common cancer was acute lymphoblastic leukemia, diagnosed in 50% (56/111) children, followed by acute myeloid leukemia in 14/111 (12.6%), brain tumors in 9 (8.1%), and neuroblastoma in 10 (9%) children. The median patient interval/patient delay was 14 days (1–90 days), referral interval was 14 days (1–150 days), and overall time to diagnosis was 41 days (1–194 days). The first contact was the pediatrician in 86/111 (77.4%). Sixty-four percent (71/111)

Keywords

- childhood cancer
- acute lymphoblastic leukemia
- Time to diagnosis
- diagnostic delay

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referral came from a secondary care hospital, and the remaining from the outpatient clinics. There was no difference in sex and patient interval ($p = 0.278$) and overall time to diagnosis ($p = 0.4169$), age ($p = 0.041$), mother's education ($p = 0.034$), and type of cancer ($p = 0.013$) were three critical factors that determined the time to diagnosis.

Conclusion Majority of the children diagnosed with cancer presented via referral from pediatricians. An equal number of them were referred to as routine and emergency patients. Age, mother's education, and type of cancers were the crucial factors associated with the overall time taken to diagnosis.

Introduction

Cancer is an important cause of death in both children and adults. Around 70% of these cancer-related deaths happen in low- and middle-income countries such as India.¹ As per the Population-Based Cancer Registry (2012–2014) report, childhood cancer accounts for 0.7 to 4.4% of total cancer diagnoses in India.^{2–5} The reported standardized incidence rate for India varies from 38 to 124 per million children per year.⁶ Childhood cancer is predominantly not amenable to preventive strategies. Over the last few decades, in the developed world, the overall cure rate of childhood cancers has been above 70%, whereas in India, we struggle to cross 50%.⁶ India's low survival is due to various factors such as presentation in an advanced stage of cancer, delay in diagnosis, poor access to treatment, treatment abandonment, poor supportive care, and poor infection control practices.^{6,7} With the significant progress in the treatment and survival of childhood cancers in the developed world, the focus has shifted to early detection to reduce the treatment-related side effects, especially for those types of cancer, which carry an excellent prognosis.^{8,9}

In the initial part of cancer, signs and symptoms could mimic the common childhood illnesses, which may cause a delay in diagnosis.^{10,11} It is essential to know the patient's pathway from the onset of symptoms to final diagnosis, to avoid a delay in diagnosis, which plays an essential role in better survival strategy.^{10–12} There are many studies published on delay in diagnosis in children with cancer in developed countries.^{9,11,13–15} However, only a few articles have been published on this subject from developing countries.^{16–19} We do not have any study from the author's region in India done on routes of presentation of childhood cancer, time to diagnosis (TTD), and time to start treatment.

Materials and Methods

It was a retrospective cohort study of 111 children diagnosed with cancer between the January 1, 2014 and December 31, 2016 (3 years) at a teaching hospital, Mangalore, India. All children aged between 0 and 18 years diagnosed with cancer during the study period were included in the study, while in those where we could not retrieve the required information were excluded. It is a private tertiary care teaching

hospital with a dedicated pediatric hematology/oncology unit, which is the only center in Dakshina Kannada district. The majority of patients are from below poverty line (BPL) as per the Government of India criteria and remaining from lower-middle socioeconomic status. The catchment area has been quite large, around 400 km but an average of 100 km. All those from BPL background received treatment under government scheme (Suvarna Arogya trust),²⁰ and others received treatment by obtaining funds from various non-government organizations or self-funds. The details of age, sex, address, distance from the treatment center, rural/urban area, parents, education status, parents economic status, number of siblings, duration of symptoms before seeing a doctor (symptom interval), time to presentation to a pediatric oncologist, TTD (diagnosis interval) and time to initiate treatment after confirming the diagnosis, and type of cancer were captured. An interview with all parents conducted in the year 2017 to collect the information not available from the case notes. The primary outcome was to know the factors affecting the overall time taken to diagnosis. The secondary outcomes were to know the patient interval, referral interval, and time taken to treatment.

Definitions (→ Fig. 1)

Patient interval^{21,22}: It is defined as the time between symptom onset and first clinical presentation. It is also called patient delay, duration of symptoms before the presentation

Referral interval: It is defined as the time from first seen by a pediatrician or a general practitioner to presentation to a pediatric oncologist.

Diagnostic interval: It is referred to the period from direct engagement with a healthcare professional to a definitive diagnosis (also referred to as doctor, physician, or healthcare delay)

Overall TTD/symptom interval: It is defined as the time from initial symptoms to diagnosis at our pediatric oncology unit. The time between symptom recognition and a definitive diagnosis was described as TTD.

Treatment interval (time to initiate treatment): It is defined as time taken to commence treatment from the diagnosis.

Time to treatment: It is defined as time from initial symptoms to commencement of treatment; whether surgery or chemotherapy.

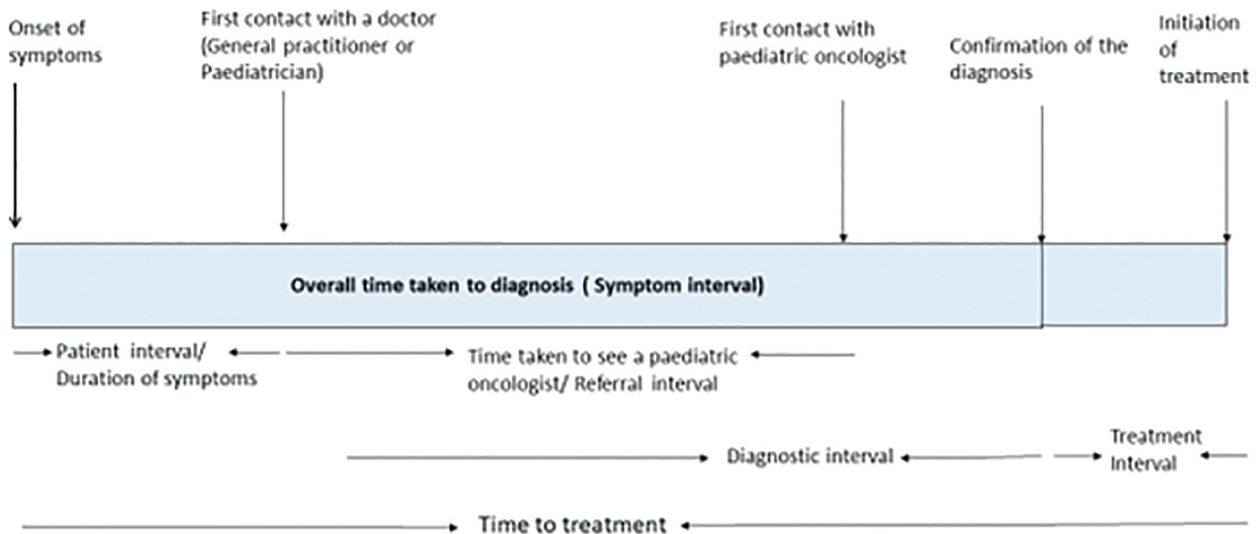


Fig. 1 Schema of patient interval, referral interval, diagnostic interval, and symptom interval.

The date of onset of symptoms and first contact with a healthcare professional were based on recall by the parents (parents interview), while the date of the first visit to the pediatric oncology center, date of confirmation of diagnosis, and date of initiation of treatment were recorded from the hospital case records.

Statistical Analysis

Univariate analysis was used to know the factors associated with total delays and assess each factor's impact separately on the patient interval, and total time taken to diagnosis. We also used it to determine correlations between possible contributing variables and time taken to diagnosis. For comparison of two groups of categorical variables, independent *t*-tests were used (as in sex variable). To compare more than two categorical variables (as in age groups, family size, father and mother's education, residence, and family income variables) one-way analysis of variance (ANOVA) was used. We used Tamhane's T2 multiple comparison tests to compare total intervals between different groups between other group pairs after ANOVA. In multivariable analysis, statistically significant variables in the ANOVA were included using a linear regression model for continuous data to estimate independent factors associated with patient interval and time taken to diagnosis. All analyses were performed using SPSS software (IBM SPSS Statistics for Windows, version 20.0, Armonk, New York, United States: IBM Corp). A *p*-value ≤ 0.05 was considered statistically significant at a 95% confidence level. The missing data were addressed by complete case wise analysis or list wise deletion.

Ethics: The Institutional Ethics Committee of Kasturba Medical College Hospital Mangaluru (IECKMCMLR09–16/245) approved this study. The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1964, as revised in 2013. Consent has been obtained initially at the time of commencement of treatment to collect the data about the family size, socioeconomic status, parents' education, and underlying type of cancer.

Results

A total of 115 children were registered with childhood cancer during the study period. We could record the details of 111 children, while we could not collect data for remaining four children due to insufficient information in the case records (►Table 1). The median duration of the patient interval, meaning onset of symptoms to the first contact of a doctor, was 14 days (95% confidence interval [CI]: 14–19; range: 1–90 days). The median duration of diagnostic interval (from the first contact of a doctor to final diagnosis by a pediatric oncologist) was 21 days (95% CI: 18–31 days). For the parents and patient, the first contact was the pediatrician in 86/111 (77.4%) patients, followed by a general practitioner in eight children; a pediatric surgeon, general surgeon and general physician saw four children each. A total of 71/111 (64%) referral came from a secondary care hospital and remaining from the outpatient clinics. Fourteen (12.6%) children were directly admitted to the intensive care unit. The referral was an emergency in 56 (50.5%) patients. There was no difference in sex and patient interval ($p = 0.278$), time to present to a pediatric oncologist, time taken to diagnosis ($p = 0.976$), ($p = 0.4169$), and time to commence treatment ($p = 0.688$) on unpaired *t*-test. The number of siblings did not make any difference in the duration of various intervals ($p = 0.16$). Forty-nine children were from families with monthly income < Rs 10,000 and 58 were from family with income of Rs 25,000 to 50,000, and rest four were from the family of income with > Rs 50,000/month. Family income was an essential factor in the patient interval ($p = 0.02$). An equal number of children were from within and outside the district. Six fathers (5.4%) and nine (8.1%) mothers were illiterate. High school level education was completed in 70/111 (64.1%) fathers and 76/111 (67.1%) mothers. On ANOVA test, only the mother's education levels were significant ($p = 0.038$) in determining the time taken to presentation to a doctor (patient interval) as well as for time taken to diagnosis (►Table 1). The majority of children 70/111 (63.8%)

Table 1 Patient factors associated with patient interval, referral interval, diagnostic interval, overall time to diagnosis, treatment interval, and time to treatment

Variables	n = 111	Patient interval median (range) in days	p-Value	Referral interval median (range) in days	p-Value	Diagnostic interval median (range) in days	p-Value	Overall time to diagnosis (symptom interval) in days	p-Value	Treatment interval median (range) in days	p-Value	Time to treatment median (range) in days	p-Value
Sex													
Male	72 (64.9%)	14 (1–90)	0.318	14 (1–150)	0.754	21 (2–165)		41 (1–194)	0.92	5 (1–120)		47.5 (6–315)	
Female	39 (35.1%)	15 (2–45)		14 (1–135)		22 (2–145)		44 (8–157)		7 (2–90)		54 (11–171)	
Age													
<5 years	51 (45.9%)	14 (5–45)	0.450	7 (1–120)	0.425	17 (2–127)	0.438	34 (7–157)	0.012	5 (2–90)	0.051	39 (9–171)	0.164
5–10 years	32 (28.8%)	14 (2–90)		21 (2–190)		26 (6–164)		48.5 (12–194)		6 (2–21)		53.5 (17–201)	
>10 years	28 (25.2%)	15 (4–30)		16 (3–105)		24.5 (3–165)		44.5 (5–195)		7 (1–120)		51.5 (6–315)	
Family size													
3	31 (27.9%)	14 (1–30)	0.792	7 (1–150)	0.148	17 (4–164)	0.079	31 (7–194)	0.16	5 (2–21)	0.700	39 (9–201)	0.153
4–5	72 (52.3%)	14.5 (2–45)		14 (2–150)		22.5 (3–160)		44 (5–190)		7 (1–30)		54 (6–195)	
>5	8 (19.8%)	14 (2–30)		14.5 (3–120)		23 (5–165)		42.5 (8–195)		7 (2–120)		50 (11–315)	
Father's education													
Illiterate	6 (5.4%)	14.5 (5–30)	0.533	10.5 (4–30)	0.533	21.5 (11–40)	0.165	35.5 (16–70)	0.169	9.5 (7–15)	0.023	44.5 (31–80)	0.094
Primary	33 (29.7%)	14 (2–45)		15 (5–105)		23 (5–165)		44 (8–195)		7 (2–120)		57 (11–315)	
High school	37 (33.3%)	14 (2–90)		10 (2–150)		19 (2–160)		42 (7–90)		5 (1–15)		47 (6–195)	
Preuniversity course	15 (13.5%)	14 (4–30)		8 (2–150)		20 (4–164)		35 (11–194)		6 (2–21)		44.5 (13–201)	
Graduation	17 (15.3%)	13.5 (5–30)		14 (2–120)		21 (6–127)		38 (13–134)		5 (2–21)		46 (16–147)	
Postgraduation	3 (2.7%)	17.5 (5–30)		72 (24–120)		79 (31–127)		96.5 (36–157)		2		159	
Mother's education													
Illiterate	9 (7.2%)	22.5 (10–30)	0.165	30 (2–35)	0.060	36.5 (12–45)	0.287	61 (27–80)	0.038	9.5 (2–13)	0.076	71 (29–93)	0.425
Primary	27 (24.3%)	15 (2–90)		14 (2–90)		21 (5–165)		42 (8–195)		6.5 (2–120)		47.5 (11–315)	
High school	33 (29.7%)	14 (2–45)		10 (2–105)		17 (4–160)		40 (8–127)		5 (3–15)		47 (11–135)	
Preuniversity course	17 (15.3%)	14 (2–21)		14 (2–150)		29 (2–160)		48 (5–175)		5 (1–21)		58 (6–182)	
Graduation	24 (21.6%)	14 (2–30)		14.5 (2–120)		21.5 (4–164)		35 (7–194)		4.5 (2–30)		41 (9–201)	
Postgraduation	1 (1.8%)	18.0		10.0		28.0		37		3		34	
Family monthly income (Rs)													
<10,000	49 (44.1%)	15 (2–90)	0.001	14 (3–150)	0.589	22 (7–165)	0.300	42 (5–195)	0.025	7 (2–120)	0.077	57 (17–315)	0.011
10,000–50,000	58 (52.2%)	14 (2–30)		11 (2–150)		20.5 (4–164)		41.5 (35–48)		5 (2–21)		46 (11–201)	
>50,000	4 (3.6%)	18.5 (1–14)		10 (1–30)		16.5 (3–142)		13.5 (7–20)		3 (1–7)		39 (6–159)	

(continued)

Table 1 (continued)

Variables	n = 111	Patient interval median (range) in days	p-Value	Referral interval median (range) in days	p-Value	Diagnostic interval median (range) in days	p-Value	Overall time to diagnosis (symptom interval) in days	p-Value	Treatment interval median (range) in days	p-Value	Time to treatment median (range) in days	p-Value
Residence	Urban	41 (36.9%)	0.617	14 (2-30)	0.617	24 (4-164)	0.653	44 (8-195)	0.97	5 (1-21)	0.341	43.5 (6-201)	0.796
	Rural	70 (63.1%)		14 (2-90)		20.5 (2-165)		40 (5-194)		6.5 (2-120)		50 (11-315)	
Distance from the hospital	< 100	70 (63.1%)	0.786	14 (2-30)	0.786	17 (3-165)	0.046	33 (5-194)	0.02	5 (2-120)	0.073	40 (6-315)	0.646
	100-250	31 (27.9%)		15 (5-90)		28 (8-164)		46 (16-194)		7 (2-90)		57 (19-201)	
	>250	10 (9%)		18 (2-30)		33.5 (12-85)		55.5 (14-110)		7 (4-13)		64 (21-115)	
District	Dakshina Kannada	55 (49.5%)	0.379	14 (2-35)	0.379	17 (3-165)	0.119	33 (7-157)	0.049	5 (1-120)	0.344	40 (6-315)	0.476
	Others	56 (50.5%)		14.5 (2-90)		27.5 (4-164)		34.5 (5-195)		7 (2-90)		53 (13-201)	
Insurance schemes	Govt insurance schemes for people with below poverty line	60 (54%)	0.849	14.5 (2-90)	0.849	25 (4-165)	0.424	50 (8-195)	0.023	7 (2-120)	0.606	52.5 (11-315)	0.038
	Self	46 (41.4%)		14 (7-30)		20 (2-164)		35 (7-157)		5 (1-15)		47 (6-201)	
	Other insurance (private)	5 (4.5%)		14 (7-21)		19.5 (4-24)		36.5 (34-49)		3 (2-7)		41 (13-52)	

Table 2 Different types of cancers and median patient interval, referral interval, diagnostic interval, symptom interval, treatment interval, and time to treatment

	<i>n</i> =111	Patient interval (days)	Referral interval (days)	Diagnostic interval (days)	Overall time to diagnosis (symptom interval) (days)	Treatment interval (median in days)	Time to treatment (median in days)
<i>p</i>-Value		0.003	0.075	0.080	0.001	0.626	0.3
Acute lymphoblastic leukemia	56 (50.4%)	14 (2–45)	11 (1–150)	18 (4–160)	33 (5–175)	5 (1–90)	38 (6–182)
Acute myeloid leukemia	14 (12.6%)	14 (1–30)	5 (1–30)	12.5 (5–34)	32 (7–49)	5 (2–14)	22 (9–54)
Brain tumors	9 (8.10%)	15 (5–35)	23 (3–120)	36 (6–127)	63 (16–157)	14 (2–21)	82 (17–159)
Neuroblastoma	10 (9.00%)	14 (5–30)	10.5 (7–30)	22 (13–40)	39 (18–65)	5 (2–8)	49 (26–72)
Lymphoma	9 (8.10%)	21 (14–90)	30 (7–150)	45 (17–165)	70 (32–195)	7 (5–60)	80 (40–315)
Others (Wilms tumors 4, Ewing's 2, osteosarcoma 2, rhabdomyosarcoma 2, JMML 2, retinoblastoma 1, teratoma 1)	13 (11.7%)	21 (7–30)	18 (1–75)	28 (2–85)	52 (9–99)	9 (2–15)	65 (29–103)

Abbreviation: JMML, juvenile myelomonocytic leukemia.

were residing in a rural area. It does not have any correlation with the TTD ($p = 0.97$). The distance from the hospital is an essential factor in the patient interval as well as for the overall time taken to diagnose ($p = 0.02$). Sixty-four children (58%) had insurance schemes, of which 60 (54%) had the government insurance schemes meant for children from an economically poor background. This factor also played important role in determining the time taken for an overall diagnosis ($p = 0.023$). The most common cancer diagnosed in 50% (56/111) patients was acute lymphoblastic leukemia (ALL),²³ followed by acute myeloid leukemia (AML) in 14/111(12.6%) children. The brain tumors were noted in nine (8.1%) and neuroblastoma in ten (9%) children. The median overall time taken to diagnosis was 70 days for lymphomas (32–195 days), 63 days for brain tumors (12–157) days, and 33 days for ALL (5–175) days (► **Table 2**). The one-way ANOVA test on comparing the means of patient interval and diagnosis, referral interval and underlying diagnosis, diagnostic interval and diagnosis, and the overall time taken to diagnosis showed that patient interval, diagnosis interval, and the overall time taken to diagnosis were significant between the different types of cancer ($p < 0.05$). The median referral interval for ALL was 11 days. The overall time to initiate treatment after diagnosis varied between 1 and 90 days with a median of 5 days for ALL (1–90), 12 days for brain tumors (2–21), 7 days for neuroblastoma (2–8), and 7 days for lymphoma (5–60) days (► **Table 2**).

Age, mothers' education, distance from the hospital, family income, insurance schemes, and underlying diagnoses were significant for patient interval and the overall time taken to diagnosis on the ANOVA test. On multivariable analysis using a linear regression model of the above variables, age ($p = 0.041$), mothers' education ($p = 0.034$), and type of

cancer ($p = 0.013$) were three critical factors that determined the time taken to diagnosis.

Discussion

Overall TTD of childhood cancer varies between cancer types. In our study, the overall time taken to diagnosis was better than the study reported by Verma and Bhattacharya.²⁴ This is likely due to primary care pediatricians and general practitioners quickly referred these children to a pediatric oncologist. Also, most of the doctors who have referred to us were working in their establishment clinics, which could have played a role in early referral. The overall time taken to diagnose was maximum for bony sarcomas and least for acute leukemias, similar to a study published by Brasme et al.²⁵ Earlier studies have shown that TTD depends on the cancer type, shortest for abdominal tumors²⁶ and the longest time for brain tumors.²⁷ The median duration of onset of symptoms to confirmation of the diagnosis in acute leukemia was 33 days. Ewing's sarcoma has one of the most prolonged intervals between onset of symptoms and diagnosis.^{22–24} Lethaby et al,¹¹ in their systematic review, found out that bone tumors and brain tumors were taking a long-time average of 100 to 110 days to diagnosis.²⁸ Stefan and Siemonsma²⁹ published a study where an average of 20 days delay was attributed to the physician. Likewise, Araz and Guler³⁰ also noted physician delay in the diagnosis. In our study, the median referral interval was 17.5 days, which was better than the rest of the published studies. This could happen because of the average education level of both parents and awareness of childhood cancer among the primary care doctors, mainly pediatricians.

Our study showed no correlation between the child's sex with patient interval or time taken to diagnosis. A few studies

published from India²⁴ showed that the female child had to wait more days to consult a doctor. Gender bias in seeking healthcare or cancer treatment has been previously reported in lower and middle-income countries, especially from India.⁶

A child's age was the most influencing factor in determining the patient interval and the time taken to diagnose. In our study, age played an important role in seeking medical advice at first and time taken to diagnosis, which is statistically significant. The older age children (>10 years) had a longer duration of symptoms before confirmation of the diagnosis. Likewise, several studies^{16,30,31} reported that older the child, more the delay in seeing a doctor and for TTD. In hematological malignancies, Venkatasai et al¹⁸ did not find any relation with delay in the child's presentation and age.

Our study showed that a mother's education plays an essential role in the time taken to diagnose. In contrast to this, study from Bangladesh by Begum et al,¹⁹ showed no relationship with the mother's education. Instead, father education played an important role in taking these children to doctors and getting the diagnosis. A study from Israel³¹ reported that working mothers took more time to see a doctor, and the father's education did not affect the patient interval. This difference in findings between our study and rest could be because of family customs or male-dominated society.

There was a statistically significant correlation between family income and time to see a doctor or TTD in our study. Similar findings were noted in Venkatasai et al¹⁸ and Begum et al.¹⁹ However, Verma and Bhattacharya²⁴ did not show any correlation with economic background. Our study, like a study by Abdelkhalek et al,¹⁷ did not reveal any correlation between the patient's places of residence, whether it was rural or urban to TTD. However, studies from the rest of India, by Venkatasai et al¹⁸ and Verma and Bhattacharya,²⁴ have found that children from rural backgrounds take a longer time to see a doctor and end up having a longer TTD. This could be because of the high literacy rate in the author's region. Some of the patients from rural backgrounds in Venkatasai's group received alternative medicine therapy, which caused a delay in diagnosis. Also, parents from rural areas were from poor socioeconomic backgrounds, and their education level was lower.

In our study, the median time required initiation of treatment was around 5 (1 to 90) days. A majority of children were from low monthly income backgrounds, and they had to wait for the approval of the application for funding for the treatment. However, there is no influential association of TTD with better survival; TTD is a factor in reducing the morbidity associated with the condition.¹¹

Diagnosis of cancer through an emergency presentation route is presumed to be an indicator of late diagnosis and a corresponding poor prognosis. In this study, an equal number of children presented to the emergency and the clinic. It did not have any impact on the patient interval or to symptom interval. There is a need to find out the extent of delay in diagnosis of cancer in across the country by doing prospective, multicenter study, and addressing the factors responsible for the same to improve the overall survival.

Limitations

It was a retrospective study and therefore subject to certain limitations inherent in their design. In addition, it had a relatively small sample size. The use of preexisting case records makes it difficult to obtain information on potential confounding variables. Parents and patients have recalled certain events, especially the onset of symptoms and first contact with a doctor.

Conclusion

Overall, our study showed a statistically significant association with the age, mother's education, and diagnosis with the patient interval and overall time taken to diagnosis. A prospective nationwide study may help to plan and implement the intervention programs to reduce delays.

Authors' Contribution

Harsha Prasada Lashkari conceived the idea, and designed, analyzed, and wrote the manuscript. Shobha Prasada helped to write the draft. Jayatheerth Joshi and Sadashiva Rao helped in referring the patients for the recruitment of the study. All the authors have approved the final version to be published and agree to be accountable for all aspects of the work.

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Conflicts of Interest

There are no conflicts of interest.

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