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Delayed referral and treatment of paediatric cancer in Nigeria: Time to stop blaming the victim

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Abstract: *Background:* Caregiver delay in presentation has been cited as a major contributor to poor prognosis of paediatric cancers in low-middle income countries like Nigeria. This study explored the time duration between onset of symptoms and presentation to healthcare facilities, diagnosis, and referral for specialist care.
Methods: Data were compiled from caregivers of newly registered children at a teaching hospital in Nigeria. Socio-demographic and clinical history of the child were taken. Type of cancer, date of diagnosis, centre where the diagnosis was made, treatment start date, and duration of symptoms until treatment were elicited from consenting caregivers and documented.
Results: Acute lymphoblastic leukaemia was the most prevalent cancer type among the patients. The mean time from first symptom to presentation was 15 weeks and from presentation at any health care facility to specialist referral and diagnosis was 38 and 39 weeks, respectively. Time from diagnosis to treatment was a mean of 8 weeks (range: 1 to 27 weeks)
Conclusion: Delayed presentation has become a commonly cited factor for poor cancer outcomes in Nigeria and may often inaccurately assign blame to the patient/ caregivers. The results of this study point to delayed detection, delayed diagnosis and delayed referral for specialist care, as more accurate contributors to late-stage presentation and consequently worse outcomes of paediatric cancers in Nigeria. Strengthening of community and primary level healthcare professionals' understanding of paediatric cancers, establishment of simple detection algorithms and national implementation of efficient referral protocols will potentially reduce delays in specialist attention and improve outcomes.

Keywords: Delayed referral, Paediatric cancer, Time Lag, Missed diagnosis

Introduction

In the last three decades, Global Cancer Incidence, Mortality, and Prevention (GLOBOCAN) data have shown that cancer has caught up to infectious disease as a leading cause of morbidity and mortality in children and adolescents in low and middle-income countries (LMICs).[1] Today, cancer is the second leading cause of childhood death in developing world, with 85% of all cases and 95% of deaths worldwide occurring in LMICs like Nigeria, where significant deficiencies in access to life-saving resources is a central contributing factor.[2]
In the early 1960s, the survival rate of childhood cancer in high income countries was about 30%. Through a combination of increased awareness and education, early detection, improved accuracy of diagnostic modalities, a deeper understanding of cancer biology, and advances in treatment modalities, survival rates for many childhood cancers now approach 80% to 100%, depending on the tumour type and stage.[3-5] Notably, these improvements are not reflected in the numbers seen in the developing world. Survival rates in LMICs like Nigeria continue to hover around the 30% mark.[6]

In contrast to many adult cancers, paediatric cancers often have better prognoses and survival rates.[7] It is widely known that many cancers that occur in children can be successfully treated, despite the many challenges that might be encountered in the care of a child with cancer.[7] However, In LMICs like Nigeria, factors such as low community awareness, delayed detection, inadequate diagnostic capability, the financial burden of cancer diagnosis and treatment, and the numerical, geographic, and financial unavailability or inaccessibility of specialist care collectively contribute to the high mortal-

ity rates among children with cancer compared to global rates.[8]

The benefit of early presentation in paediatric cancers cannot be overemphasised. Primarily due to the non-specific symptoms of paediatric cancers, efforts have been invested globally to increase community awareness and improve health-seeking behaviour among parents/ caregivers. Heightened awareness should translate to early-stage identification and detection of disease, which helps ensure better outcomes for children.[9] These efforts may, however, be moot if early presentation is not matched with equally prompt and properdetection, diagnosis and treatment.[10] In practise, it is not uncommon to see children presenting with advanced-stage disease, effectively assigning them a poor prognosis before intervention even begins.

Delayed presentation of paediatric cancer patients in Nigeria due to caregiver decisions and factors have been well documented over the years.[11,12] Factors including patient or caregiver's age, sex, birth order, socioeconomic status, educational level, and religious and sociocultural beliefs have all been well-explored as contributors to delayed presentation.[10] On the other hand, health sector factors including a poor index of suspicion leading to late detection by healthcare providers, misdiagnosis, missed diagnoses, and delayed referral to specialist care have been less explored, leading to a tendency to 'blame the victims.[13] This study examined time duration between the first encounter with any healthcare professional for cancer-related symptoms, to diagnosis and/or referral for specialist care; for children presenting to the Paediatric Oncology unit of the Lagos University Teaching Hospital. The study design involved structured interviews of caregivers of children affected by cancer to ascertain factors that may contribute to delays in detection, diagnosis and treatment initiation.

Subjects, materials, and methods

This study was a cross-sectional survey carried out at the Paediatric Oncology Unit of the Lagos, University Teaching Hospital, Lagos, Nigeria between January 2019 and January 2020. Lagos University Teaching Hospital (LUTH) is the foremost tertiary hospital in Nigeria, the most populated country in Africa. The hospital serves the 21 million population of Lagos, the most densely populated state in Nigeria. As the oldest and most prominent tertiary hospital located in the commercial centre of the country, LUTH also regularly receives referrals from other Nigerian states.

Caregivers of all newly registered children with histologically diagnosed cancer seen during the study period were approached for the study. Children with relapsed disease or who had already been treated at the unit were excluded from the study. Patients aged 18 years and older and those whose caregivers did not consent to the study were also excluded. Once eligibility was determined, consecutive sampling methodology was used in patient recruitment until the study period elapsed.

A summary of the study, its objectives and procedures were explained to each parent or caregiver. Informed consent was obtained from caregivers, and assent from children aged seven years and above. With each new presentation, a pre-designed, structured, interviewer administered questionnaire was used to obtain information from the parent(s)/caregiver(s). The questionnaire was adapted from results of previous studies on similar subjects and was then pretested to ensure its ability to curate data to answer the research questions.[14-17] As different tumour types in children were considered, tumour staging was reported as 'early stage' and 'advanced stage.' Advanced stage disease was described as stage III and IV for Wilms tumour, Lymphoma, Neuroblastoma, Retinoblastoma, Rhabdomyosarcoma and Lymphoma. The Ogunlesi's modification of Oyedeji's social class was used to categorise participants in initial five groups depending on parents' educational status and occupation and then group into 'high', 'low', and 'middle' classes.[18] Information collected included the age and sex of the patient, family size and structure, number of siblings, socio-demographic and economic characteristics of caregivers, clinical history of the patient, specifics relating to the cancer diagnosis, timelines, and factors associated with any delays surrounding the diagnosis. The time period information collected was split into two broad groups; 'time from first symptom' and 'time from first presentation to a healthcare professional (HCP).'

Data were analysed using the Statistical Package for Social Sciences version 23 software (SPSS, Chicago, IL). Unless otherwise stated, a p-value of <0.05 was considered significant. Univariate analysis using frequency tables, percentages mean, and the standard deviation was used to present socio-demographic variables such as age, sex of the patient, family size and clinical history of patients. Bivariate analysis using the student t-test or ANOVA was used to compare the association between factors that may be statistically associated with time duration. Ethical approval was obtained from the Ethics Committee of the Lagos University Teaching Hospital, and the study was conducted according to the principles of the Helsinki Declaration. Consideration was made for data confidentiality, non-male ficence, and beneficence.

Results

A total of 49 children with histologically diagnosed cancer whose parents consented to the study were recruited and reviewed; out of a total of 71 new paediatric cancer patients who were approached over the one-year period, 22 caregivers declined to participate. There was a significant male preponderance (34, 69%) with age distribution from 2months to 17years. The mean age of study participants was 5.3 years (Table 1). In the majority of families of the study participants, there were at least two

other children in addition to the patient diagnosed with cancer. More than one-quarter of the patients seen (26, 32.7%) were cared for by single parents. Referrals from a health facility in rural areas across the country accounted for less than a quarter (7, 14.3%) of patients presenting at LUTH (Table 1). The caregivers of the study participants were mostly formally educated (secondary level) and earned less than ₦150,000 ($411 USD) monthly (Table 2).

Table 1: Socio-demographic and clinical characteristics of study participants

Variable (n=49)	n (%)		n (%)
Socio-demographic characteristics		Clinical History	
Age		First symptom	
Mean ± SD	5.3 ± 2.1 years	Recurrent infection	5(10.2)
Sex		Bleeding	2(4.1)
Male	34(69.4)	Painless swelling	22(44.9)
Female	15(30.6)	Painful swelling	2(4.1)
Number of siblings		Weight loss	5(10.2)
None	4(8.1)	Others	15(30.6)
One	8(16.3)	Place of first contact	
Two	10(20.4)	Private hospital	27(55.1)
Three	17(34.7)	Primary health centre	12(24.5)
Four	7(14.3))	General hospital	8(16.3)
Five	3(6.1)	Tertiary centre	2(4.1)
Family structure		Number of facilities visited before specialist care	
Both parents	33(67.3)	1	11(22.5)
Single parent (Father)	5(10.2)	2-4	33(67.3)
Single parent (mother)	11(22.5)	5 or more.	5(10.2)
Home Location		Place of diagnosis	
Rural	7(14.3)	Private hospital	2(4.1)
Urban	42(85.7)	General hospital	11(22.4)
Parents' religion		Tertiary hospital	36(73.5)
Christianity	31 (63.3)	Referral letter at presentation	
Islam	18(36.7)	Yes	28(77.6)
Parents' Ethnicity		No	21(22.4)
Yoruba	39(79.6)	Stage at presentation	
Hausa	2(4.1)	Early stage	2(4.1)
Igbo	6(12.2)	Advanced stage	47(95.9)
Others*	2(4.1)		

*Others include Tiv, Calabar

Table 2: Socioeconomic characteristics of caregivers

Variable (n=49)	n (%)
Health insurance	
Yes	0(0.0)
No	100(0.0)
Level of education of primary caregiver	
None	9(18.4)
Primary	8(16.3)
Secondary	21 (42.9)
Tertiary	11(22.4)
Family's estimated monthly income	
< N18,000 ($49)	5(10.9)
N18,000 - < N50,000 ($49- <$137)	12(26.1)
N50,000 -N150,000 ($137 - $411)	26(56.5)
> N 150,000 (>$411)	3(6.5)
Socioeconomic class	
Low	16(32.7)
Middle	29(59.2)
High	4(8.2)

Acute lymphoblastic leukaemia (ALL) was the most prevalent cancer type seen among the patients recruited. The most common first symptom among study participants was a painless swelling, seen in almost half (22, 44.9%) of the study participants. Over half (27, 55.1%) of study participants first presented at a private hospital, but they were subsequently diagnosed at a tertiary centre (36, 73.5%). Almost all (47, 95.9%) of patients had advanced disease at the time of the first presentation to the specialist centre.

On average, it took caregivers 15 weeks from noticing the first sign or symptom of illness in the child to presentation to a healthcare facility, with durations ranging from 1 week to 28 weeks. The mean time from the first presentation to a healthcare facility to the diagnosis of cancer was 39 weeks, with durations ranging from 12 weeks to 53 weeks. The time from the first presentation at a healthcare facility to referral for specialist care was 38 weeks, with durations ranging from 9 weeks to 57 weeks. Time from diagnosis to treatment took a mean of 9 weeks (1 week to 27 weeks) (Table 3). Following presentation to a healthcare provider, there was an association between factors such as socioeconomic and educational status, place of residence, first symptom, tumour type, place of first visit; and the time duration from symptom onset to diagnosis and referral for specialist care (Table 3).

Table 3: Time interval by diagnosis

Tumour Type (time in weeks)	First symptom to presentation	First symptom to diagnosis	First symptom to referral	First symptom to treatment
CNS Tumours	13.7 ± 10.6	34.7 ± 8.6	31.8 ± 5.7	54.2 ± 12.0
Leukaemia	11.2 ± 6.6	61.6 ± 6.6	65.6 ± 6.6	67.7 ± 6.7
Lymphoma	20.8 ± 3.2	59.5 ± 3.0	56.3 ± 3.0	62.5 ± 3.8
Neuroblastoma	13.0 ± 9.9	47.4 ± 10.1	44.2 ± 10.0	61.0 ± 4.1
Osteosarcoma	12.5 ± 13.4	58.8 ± 15.2	62.8 ± 15.2	67.0 ± 11.3
Others	16.3 ± 1.0	53.0 ± 1.5	49.8 ± 1.5	57.5 ± 1.9
Retinoblastoma	10.3 ± 9.7	40.8 ± 9.6	37.6 ± 9.5	60.3 ± 3.0
Rhabdomyosarcoma	20.0 ± 4.7	54.3 ± 4.5	51.1 ± 4.5	63.4 ± 3.6
Wilms tumour	20.8 ± 5.9	60.7 ± 7.0	58.7 ± 8.2	63.8 ± 6.0
Overall mean	15.2 ± 7.7	54.1 ± 11.2	53.2 ± 13.1	62.8 ± 7.2
ANOVA	2.090	9.939	14.468	2.706
P-value	0.060	<0.001	<0.001	0.018
Tumour Type	Presentation to diagnosis	Presentation to referral	Presentation to treatment	Diagnosis to treatment
CNS	21.0 ± 7.5	18.1 ± 7.4	40.5 ± 3.5	19.5 ± 8.7
Leukaemia	50.5 ± 1.7	54.5 ± 1.6	56.6 ± 2.1	6.1 ± 0.7
Lymphoma	38.6 ± 0.6	35.4 ± 0.6	41.7 ±1.4	3.0 ± 1.8
Neuroblastoma	34.4 ± 0.5	31.2 ± 0.5	48.0 ± 7.2	13.6 ± 7.4
Osteosarcoma	46.3 ± 1.8	50.3 ± 1.8	54.5 ± 2.1	8.3 ± 3.9
Others	36.8 ± 0.6	33.6 ± 0.6	41.3 ± 2.5	4.5 ± 2.7
Retinoblastoma	30.5 ± 0.4	27.3 ± 0.5	50.0 ± 8.9	19.5 ± 8.9
Rhabdomyosarcoma	34.3 ± 2.0	31.1 ± 2.0	43.4 ± 3.4	9.1 ± 3.2
Wilms tumour	39.9 ± 3.7	37.9 ± 6.3	42.9 ± 4.9	3.1 ± 2.4
Overall mean	38.8 ± 9.4	38.1 ± 12.3	47.5 ± 7.5	8.7 ± 1.2
ANOVA	56.680	71.973	14.635	10.141
P-value	<0.001	<0.001	<0.001	<0.001

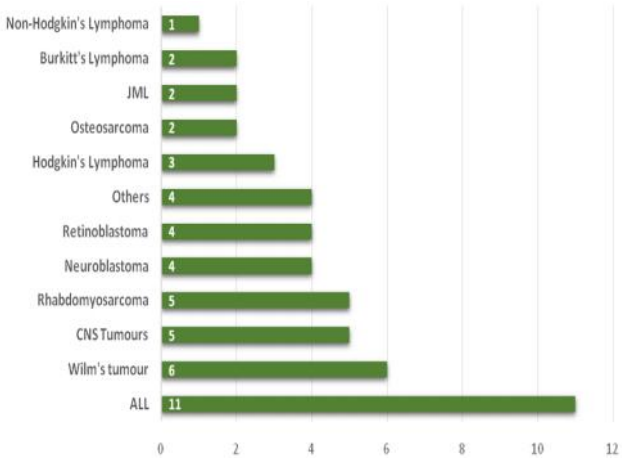
Table 4a: Socio-demographic Factors influencing time to diagnosis & referral for specialist care

Variable (n=49) Mean time from first presentation to HCP	N	To Diagnosis	p	To Referral	p
Age		(weeks)		(weeks)	
<2	5	39.1 ± 8.2		38.8 ± 12.0	
2-<5	15	40.3 ± 11.4	0.646	39.9 ± 14.5	0.552
5-<10	19	39.4 ± 8.9		38.9 ± 12.1	
≥10	10	35.4 ± 8.3		33.1 ± 9.4	
Sex					
Female	15	39.4 ± 7.9		38.2 ± 10.8	
Male	34	38.6 ± 10.2	0.773	37.9 ± 13.1	0.953
Family structure					
Single Parent	16	36.4 ±10.7		35.0 ± 13.3	
Both parents	33	40.0 ± 8.7	0.214	39.4 ± 11.7	0.244
Socioeconomic class					
Low	16	49.7 ± 2.3	<0.00	53.7 ± 2.3	
Middle	29	35.6 ± 3.3	1	32.4 ± 4.2	0.001
High	4	18.8 ± 6.4		16.0 ± 6.3	
Educational status of primary caregiver					
None	9	51.3 ± 0.9		55.3 ± 0.9	
Primary	8	46.9 ± 2.2	<0.00	50.0 ± 4.5	
Secondary	21	36.8 ± 1.7	1	33.6 ± 1.7	<0.001
Tertiary	11	26.5 ± 7.2		23.5 ± 7.0	
Location					
Urban	42	36.7 ± 8.5	<0.00	35.1 ± 10.7	
Rural	7	51.6 ± 0.7	1	55.6 ± 0.7	<0.001

Table 4b: Clinical Factors influencing time to diagnosis & referral for specialist care

Variable (n=49) Mean time from first presentation to HCP	N	To Diagnosis	p	To Referral	p
First symptom					
Painless swelling	21	35.4 ± 7.0		32.6 ± 8.0	
Painful swelling	2	40.8 ± 6.0		41.2 ± 11.1	
Weight loss	5	45.4 ± 6.9	0.005	46.5 ± 10.5	0.0
Recurrent infections	5	49.9 ± 1.0		53.9 ± 1.0	01
Bleeding	2	48.0 ± 1.4		52.0 ± 1.4	
Others	14	36.1 ± 11.5		35.0 ± 14.3	
Diagnosis					
Leukaemia	13	50.5 ± 1.6		54.5 ± 1.6	
Lymphoma	6	38.6 ± 0.6		35.4 ± 0.5	
Rhabdomyosarcoma	5	34.3 ± 2.0		31.1 ± 1.9	
Retinoblastoma	4	30.5 ± 0.4	<0.00	27.3 ± 0.4	<0.
Neuroblastoma	4	34.4 ± 0.5	1	31.2 ± 0.5	001
Wilm's tumour	6	39.9 ± 3.7		37.9 ± 6.4	
Osteosarcoma	2	46.3 ± 1.8		50.3 ± 1.8	
CNS tumours	5	21.0 ± 7.5		18.1 ± 7.4	
Others	4	36.8 ± 0.6		33.6 ± 0.6	
Place of first visit					
Private hospital	27	38.3 ± 4.0		36.2 ± 6.3	
Primary health centre	12	50.8 ± 1.3	<0.00 1	54.8 ± 1.3	<0. 001
General hospital	8	28.9 ± 2.9		25.8 ± 2.7	
Tertiary centre	2	13.3 ± 1.1		10.5 ± 1.1	
Number of facilities					
1	11	41.4 ± 8.6	0.568	40.9 ± 11.7	0.6 50
2-4	33	37.9 ± 9.9			
5 or more.	5	38.8 ± 9.5			

Fig 1: Case Distribution



*ALL- Acute Lymphoblastic Leukemia
JMML- Juvenile myelomonocytic Leukemia
Others- Mixed Germ Cell Tumour, Myxoid Liposarcoma And Nephroblastoma
CNS Tumours- Medulloblastoma, Glioma, Intracranial Germ Cell Tumour, Primitive Neuroectodermal Tumour, Astrocytoma

Discussion

There has been extensive documentation of delayed presentation of patients with cancer in LMICs such as Nigeria over the years. The clinical workflow associated with cancer treatment includes a sequence of events beginning with recognition of symptoms, presentation for medical evaluation, diagnosis, and treatment. The Nigerian health care system needs to delineate causal factors that contribute to late-stage diagnosis so they can be constructively addressed, leading to earlier stage diagnosis and intervention. Delay by grassroots community practitioners was typical in this study. Perhaps owing to the prevalence of infectious diseases in Nigeria, in this study, the diagnosis of ALL (Acute Lymphoblastic Leukaemia) took the longest to make—a mean of 50 weeks. The primary symptom in the majority of the children with ALL studied was recurrent infection or fever, often misdiagnosed as malaria and/or typhoid fever by healthcare providers. This occurred at the primary and, many times, even at secondary healthcare levels. By contrast, in Italy, the median time from first symptom to diagnosis was 29 days (4 weeks) (IQR: 18 to 44 days) for ALL and 14 days (9-24 days) for AML (Acute Myeloid Leukaemia), as compared to the median time of 64 weeks (IQR: 58 to 69.5 weeks) seen in this study.[19] For children with osteosarcoma, a misdiagnosis of osteomyelitis or sickle cell disease was often made erroneously and repeatedly before the accurate diagnosis of sarcoma was confirmed. Most of the participants in this study had visited at least one healthcare facility before referral to a tertiary centre for specialist care (median 2-7 facilities).
The type of healthcare facility of first presentation/ contact impacted the time to diagnosis and/or referral. In children who presented at primary health centres and private hospitals, time to diagnosis and/or time to referral for specialist care was comparatively longer than in

children who first presented at a secondary or tertiary health centre. This finding could highlight the need for increased training for healthcare professionals working at the primary and/or community level to ensure early detection and suspicion of cancer in children, reduction in missed and mis- diagnoses, and increased timely referral. Even in situations where the capacity for diagnosis was present, patient factors—such as a lower socioeconomic class and lack of financial capacity for diagnostic testing—increased time to diagnosis. Not uncommonly, despite referral to specialist centres, parents and caregivers often waited weeks until funds were available to present to the specialist centre for care. Predictably, none of the study participants had health insurance, as previously reported.[20]

The educational status, socioeconomic class, and place of residence of parents/caregivers all contributed in the time to diagnosis and referral of paediatric cancer cases for specialist care in this study. However, in focusing only on delays due to caregiver factors and neglecting the role of the healthcare system in advanced stage presentation and poor outcomes of children with cancer in Nigeria, the broader scope of contributory factors remains undefined. In order to achieve increased survival rates of paediatric cancer in Nigeria, a multi-faceted approach involving multiple key stakeholders is needed. It is however worth noting that delayed presentation is not entirely absent and continues to plague children with cancer in Nigeria. On average, children first presented to a healthcare facility or professional 15 weeks after the first symptom was noted by a caregiver, contributing to an advanced stage of disease by the time of diagnosis. In a similar study conducted in by Buckle et al. that assessed 82 children with Burkitt's lymphoma, the median time from the first symptom to presentation was 9.0 weeks (range: 3.6 to 15.7 weeks) in Kenya and 12.9 weeks (range: 4.3 to 25.7 weeks) in Uganda, all lower than the median of 17.0 weeks (range: 0.5-28.0) seen in this study. The most common reasons noted by Bucke et al. for the delay was the caregiver's perception of the first symptom as attributed to either a spiritual or superstitious causes, injury, or infectious disease.[21]

The findings of this study underscore the need for reprioritisation of preventive and interventional programs directed at the reduction of paediatric mortality and morbidity rates in Nigeria; to include measures targeted towards community and primary healthcare professional training on identification and detection of the common symptoms and signs of the most commonly occurring paediatric cancers. Improving accessibility to health insurance coverage would also potentially improve time to diagnosis and treatment. While financial constraints may need be taken into account when examining the broader picture, the sharp disparity between the mean time to presentation (15 weeks) and mean time from presentation to diagnosis (38 weeks) and treatment (48 weeks) may indicate that healthcare system failures are a larger contributing factor to delayed presentation to specialist care and the consequent poor outcomes; than caregiver delays. As such, even in the face of improvement in health literacy of the population, deficiencies in the healthcare system and access disparity due to economic factors emerge as important factors that contribute to late stage diagnosis, and the consequent high morbidity and mortality in the context of childhood cancers. Even on a global stage, this is a well-recognised problem which has provoked initiatives by key stakeholders, some of which were targeted at developing countries like Nigeria.[22]

Despite these efforts, this report underscores the need for multi-stakeholder initiatives to improve outcomes associated with childhood cancers in Nigeria; in order to bring prognosis and survival into range with those observed globally. The authors acknowledge that a potential limitation of this study is the small study size, while noting there is a relatively low stream of childhood cancer cases seen at the centre if comparing to high income countries. In a recent review of all paediatric cancer cases seen at the same centre between 2015-2017, a total of 178 children were seen and managed within the three-year period; averaging about 59 to 89 cases a year. As such, the sample size reported is not out of place for the centre.[20]

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