

## Original Research Article

# Predictors of mortality and loss to follow up among children with malignancies in a resource constraint community in Nigeria

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### ABSTRACT

**Background:** Childhood malignancies are on the increase globally and are of public health concern with associated poor outcome in resource constraint settings. The objective of the study was to determine the factors associated with in-hospital mortality in children with malignant tumours, the predictors of mortality and those of loss to follow up.

**Methods:** A 2 year prospective survey of children aged 1 month-14 years admitted into the paediatric ward of Usmanu Danfodiyo University Teaching Hospital (UDUTH) Sokoto with histologic diagnosis of malignant tumour.

**Results:** There were 26 (74.3%) males and 9 (25.7%) females diagnosed of malignant tumours with male:female=3:1 and mean age at presentation of 6.8±4.0 years. Majority 25 (71.4%) were from low social class. Twenty-four (68.6%) of the subjects had metastasis at presentation. Tumours diagnosed were mainly nephroblastoma 12 (34.3%), rhabdomyosarcoma 09 (25.7%), retinoblastoma 4 (11.4%), and leukaemias 4 (11.4%). Eighteen (51.4%) subjects were discharged after initial course of treatment 15 (42.9%) died and 02 (5.7%) left against medical advice. Of the 18 subjects that were discharged, 16 (88.9%) were lost to follow up. Shock (p=0.01), multiple organ failure (p=0.02), hyperleucocytosis (p=0.04), acute kidney injury (p=0.04) and metastatic disease (p=0.04) were associated with in-hospital mortality. On logistic regression analysis, shock (p<0.001), multiple organ failure (p=0.04) and hyperleucocytosis (p=0.04) were independent predictors of mortality. Residence outside the study location was associated (p=0.04) with loss to follow up.

**Conclusions:** The high in-hospital mortality and loss to follow-up in this study can be reduced by prompt identification and management of oncologic emergencies, and the provision of support services to the children and their caregivers.

**Keywords:** Malignancy, Children, Nigeria, Mortality factors, Follow-up

### INTRODUCTION

Childhood malignancies are said to be on the increase globally and are of public health concern with associated poor outcome in resource constraint settings.<sup>1</sup> There seem to have been more attention on cancers among adults especially in Africa, with efforts geared towards robust disease control, monitoring and evaluation.<sup>2</sup> Cancer among children in Nigeria is yet to be prioritized possibly

because of its apparent low incidence in comparison to infectious diseases like malaria, pneumonias and diarrhoeal diseases.<sup>3-5</sup> In well-resourced countries, the increasing incidence of cancers have been linked to better diagnostic techniques and increasing exposure to environmental agents.<sup>6,7</sup>

It is possible that many more children in our communities become affected by malignant tumors and die from it without a proper diagnosis and treatment. The lack of a

childhood cancer registry in our setting further makes it difficult to ascertain the actual burden of the disease.<sup>8</sup> Cases that eventually present to health facilities portend poor prognosis with increasing mortality from the disease. High rates of mortality have been variously reported by studies conducted in Nigeria and beyond, and have been attributed to late presentation and diagnosis, limited treatment options, lack of manpower, specialized facilities and palliative support, with the burden of treatment mainly born by the caregivers.<sup>9-18</sup> In well-resourced countries with better management techniques, newer, more potent drugs and adjuvant therapies, the outcome has been encouraging with about 7-8 out of every 10 children with cancer achieving cure.<sup>19-21</sup>

Long term follow up of cancer cases is also a challenge in resource constraint settings like ours. Reports have shown a significant number of cases being lost to follow up in the course of managing children with malignancies.<sup>9,14,22</sup> Like any other chronic illness, the treatment of children with cancer could be time consuming and associated with increasing financial, material and other healthcare demands, in addition to increased risk of caregiver burn-out. In the absence of support by the family, community, government and other stakeholders, it becomes almost impossible to cope with the aforementioned demands. The implication of dropping out of treatment is the increase in the risk of mortality in children in whom control or remission had been achieved earlier or worsening of symptoms and mortality in children that are yet to achieve remission.

An observation of a rising trend of children presenting to UDUTH, Sokoto with advanced cases of childhood cancers, and the rate at which those discharged home for subsequent follow up visits eventually dropped-out of treatment protocols made it imperative to conduct this study, with the aim of determining the factors associated with in-hospital mortality, the predictors of mortality and those of loss to follow up. It was hoped that information from this study would enlighten healthcare providers managing the affected children and their caregivers on factors that could increase in-hospital mortality. Prompt identification of the risk factors of mortality was by extension, needed to heighten the suspicion of the managing teams as to expect deterioration in patients' condition if left unchecked and to result in stepping up in-patient care to avert mortality where feasible. Factors associated with loss to follow up if identified was to bring to fore, the need for the involvement or for more commitment by all stake holders in ensuring sustained efforts to successfully treat or hopefully cure children suffering from malignancies in the study location and possibly beyond.

## **METHODS**

The study was conducted at the paediatric ward of the department of paediatrics, UDUTH, Sokoto. The hospital is a tertiary health facility located in Sokoto, the capital

of Sokoto state, North-Western Nigeria. The hospital receives referrals from Sokoto, Kebbi, Zamfara, Niger and Katsina states of Nigeria and neighbouring Niger and Benin Republics. The paediatric ward of UDUTH is a 30 bedded unit designed to admit medical conditions occurring in children aged 1 month to less than 15 years, with an average annual admission rate of 1,450 patients. Children with clinical features or laboratory diagnosis of malignancies are managed by general paediatricians and nurses in one of the rooms dedicated to oncology cases in the paediatric ward of UDUTH.

## **Study design and subjects**

The study was a prospective survey of children with the diagnosis of malignancy consecutively admitted into the paediatric ward of the department of paediatrics UDUTH over a 2 years period from January 2017 to December 2018. The inclusion criteria for subjects were age 1 month to 14 years, histologic diagnosis of malignant tumour, an informed written consent from the caregiver and assent from children aged above 7 years. Children with malignancies exclusively managed in other departments in UDUTH were not included in this study. In the absence of a precise length of duration defined as late presentation in the literature to the best of the investigators knowledge, presentation to the hospital with clinical features of advanced disease was considered as late presentation in this study. Metastases was identified based on clinical findings and/or radiological evidence. In-hospital mortality involved cases with histologic diagnosis of malignant tumour who succumbed to illness in the course of initial admission before or after commencement of treatment. Patients who had stopped attending follow-up visits in the 6 months preceding the study were considered lost to follow-up.<sup>14</sup>

## **Data collection**

Subjects that satisfied the inclusion criteria were recruited into the study. Designed pretested questionnaires were used to document information obtained from the subjects and or caregivers which included age, gender, address, ethnicity, and socio-economic status was determined using Oyediji classification in which there is a scale for scoring the level of education and occupation of caregiver and the mean of the scores to the nearest whole number gives the socio-economic class assigned to the child.<sup>23</sup> A score of one and two, three, four and five represents high, middle and low socioeconomic classes respectively. The duration of illness before presentation to UDUTH was noted. Other information sought were history of recurrent fever, swellings, pain, bleeding, anorexia, vomiting, passage of loose stools, cough, difficulty in breathing, malaise, myalgia, arthralgia, arthritis, skin changes, headache, visual or hearing impairment, body weakness, convulsion, loss of consciousness, weight loss as well as histories of medications, surgery or other interventions prior to presentation. Physical examination (general and systemic) of the subjects was carried out and caregivers

were counselled on the possibility of malignancy, the requirements for diagnosis, treatment and duration of treatment, possible complications and outcome as well as follow-up visits for survivors. Laboratory work up included histology of tissue specimen obtained via incisional or excisional biopsy, fine needle aspirates and bone marrow aspirates. Other investigations included serum electrolytes, urea and creatinine, serum uric acid, complete blood count, peripheral blood film, serum calcium, magnesium and phosphate, liver function test, and radiologic investigations. Flow cytometry, immunohistochemical analysis and molecular diagnostic investigations were not readily available in the study location. Treatment received were chemotherapy, a combination of chemotherapy and surgery, and supportive treatment. Some patients succumbed to illness or left against medical advice before definitive treatment could be commenced. The duration of hospital stay was also noted. Patients who survived were readmitted at intervals for the continuation of treatment, re-evaluation and monitoring.

#### **Ethics statement**

Ethical approval for the study was sought and obtained from the health research and ethics committee of UDUTH, Sokoto before the commencement of the study. Written informed consent was obtained from the parents or caregivers of the children and assent was sought from children of sufficient age. The data obtained were treated with utmost confidentiality.

#### **Statistical analysis**

Statistical package for social sciences (SPSS) version 23.0 was used to analyze the data. Data entered was carefully checked to eliminate multiple or wrong entries and outliers. The prevalence of malignancy was presented as percentage while the age distribution of the subjects was analyzed and expressed as mean and standard deviation. Frequency distribution tables were used to illustrate results. Chi square test was used to determine the association between two categorical variables and Fischer's exact test was used as applicable. Logistic regression analysis was used to determine the predictors of early deaths and loss to follow up. The level of statistical significance was set at 5%, which is  $p < 0.05$ .

## **RESULTS**

#### **Demographics of the subjects**

Thirty-five of the 2,765 children admitted during the study period were diagnosed histologically of malignant tumours, giving a prevalence of 12.7 cases per 1000 children. Twenty-one (60.0%) of the subjects resided in locations away from the study area. There were 26(74.3%) males and 9(25.7%) females giving a M: F of approximately 3:1. The mean age at presentation was 6.8 ± 4.0 years, their ages ranged from 1-14 years. Majority

14(40.0%) of them belonged to age category of less than 5 years. Most 25(71.4%) subjects were from low socio-economic class (Table 1).

#### **Distribution of tumour types among patients**

The commonest tumours diagnosed were mainly nephroblastoma in 12(34.3%) patients, rhabdomyosarcoma 9(25.7%), retinoblastoma 4(11.4%), and leukaemias 4(11.4%). (Figure 1). Solid tumours were commoner 14(40.0%) in those less than 5 years of age with none of them having haematologic cancers. Fifty percent each of cases of nephroblastoma and retinoblastoma were distributed among males and females, with all cases of rhabdomyosarcoma occurring in males alone. Twenty-four (68.6%) of the subjects had metastatic disease at presentation. Majority 16(45.7%) of the subjects presented to UDUTH after 1 to 3 months of onset of symptoms, 15(42.9%) presented after 3 months, and 4 (11.4) presented before 1 month of onset of symptoms.

#### **Treatment and outcome of cases**

Duration of hospital admission ranged from 4-64 days, with a median duration of 20 days. Twenty-five (71.4%) subjects received chemotherapy, 4(11.4%) received a combination of chemotherapy and surgery, 6(17.1%) received only supportive treatment before leaving against medical advice or succumbing to illness. None of the patients received radiation therapy as those that needed it could not afford the cost. Of the 35 subjects that were enrolled, 18(51.4%) were discharged after initial course of treatment with the plan of readmission as soon as subsequent courses of treatment were due, 15(42.9%) of them died, and 2(5.7%) left against medical advice. Of the 18 subjects that were discharged, 16(88.9%) were lost to follow up at intervals, with the range of treatment courses before being lost to follow up of 1 to 8 courses. Two (11.2%) cases were in remission as at their follow up visit 2 months ago.

#### **Complications encountered by the subjects**

The main complications that occurred among the subjects were sepsis 12(34.3%), malnutrition 12(34.3%), electrolyte derangements 12(34.3%), acute kidney injury 6(17.1%), shock 5(14.3%), multiple organ failure 4(11.4%), respiratory failure 3(8.6%), hyperleucocytosis 4(11.4%), bone marrow suppression 3(8.6%), treatment related complications 2(5.7%) and disseminated intravascular coagulopathy 1(2.9%).

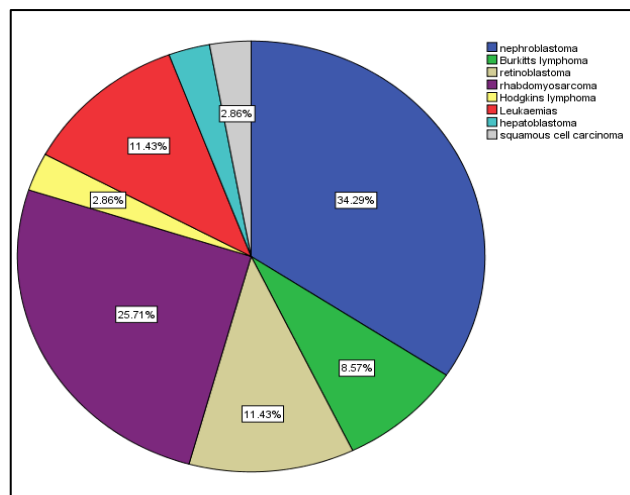
#### **Factors associated with in-hospital mortality**

There was association between the development of shock ( $p=0.01$ ), multiple organ failure ( $p=0.02$ ), hyperleucocytosis ( $p=0.04$ ), hyperkalaemia ( $p=0.03$ ), acute kidney injury ( $p=0.04$ ), and metastatic disease ( $p=0.04$ ), with in-hospital mortality. There was no

association between age group category (p=0.09), gender (p=0.39), social status (P=0.24), duration of admission (p=0.44), bone marrow suppression (p=0.40), bleeding (p=0.07), sepsis (p=0.39), malnutrition (p=0.60), and type of tumour (p=0.10), with in-hospital mortality (Table 2).

**Independent predictors of in-hospital mortality**

The factors that were found to be associated with in-hospital mortality on chi-square analysis were further subjected to logistic regression analysis. In-hospital mortality was considered as the outcome variable. The independent variables were the occurrence of shock, multiple organ failure, metastatic disease at presentation, hyperleucocytosis, hyperkalaemia and acute kidney injury. Logistic regression analysis showed that shock (p<0.001), multiple organ failure (p=0.04) and hyperleucocytosis (p=0.04) were independent predictors of in-hospital mortality among the subjects (Table 3).



**Figure 1: Types of tumours diagnosed in study subjects.**

**Table 1. Sociodemographic characteristics of the subjects (N=35).**

Characteristics	Frequency (N)	Percentage (%)
<b>Age group (in years)</b>		
<5	14	40.0
5-10	13	37.1
>10	08	22.9
<b>Gender</b>		
Male	26	74.3
Female	09	25.7
<b>Ethnicity</b>		
Hausa	33	94.3
Others	02	05.7
<b>Socio-economic status</b>		
Upper	02	05.7
Middle	08	22.9
Lower	25	71.4

**Table 2: Factors associated with in-hospital mortality.**

Variables	Death (%)	Survival (%)	Chi square (X <sup>2</sup> )	DF	P value
<b>Age group (in years)</b>					
<5	03 (21.4)	11 (78.6)	4.644	2	0.09
5-10	08 (61.5)	05 (38.5)			
>10	04 (50.0)	04 (50.0)			
<b>Gender</b>					
Male	12 (46.2)	14 (53.8)	0.449	1	0.39*
Female	03 (33.3)	6 (66.7)			
<b>Socio-economic status</b>					
Upper	00 (00.0)	02 (100.0)	2.844	2	0.24
Middle	05 (62.5)	03 (37.5)			
Lower	10 (40.0)	15 (60.0)			
<b>Metastasis</b>					
Yes	16 (66.7)	08 (33.3)	2.828	1	0.04*
No	04 (36.4)	07 (63.6)			
<b>Sepsis</b>					
Yes	06 (50.0)	06 (50.0)	0.380	1	0.39*

Continued.

Variables	Death (%)	Survival (%)	Chi square (X <sup>2</sup> )	DF	P value
No	09 (39.1)	14 (60.9)			
<b>Malnutrition</b>					
Yes	05 (41.7)	07 (58.3)	0.011	1	0.60*
No	10 (43.5)	13 (56.5)			
<b>Shock</b>					
Yes	05 (100.0)	00 (00.0)	7.778	1	0.01*
No	10 (33.3)	20 (66.7)			
<b>Acute kidney injury</b>					
Yes	05 (83.3)	01 (16.7)	1.676	1	0.04*
No	10 (34.5)	19 (65.5)			
<b>Multi-organ failure</b>					
Yes	04 (100.0)	00 (00.0)	6.022	1	0.02*
No	11 (35.5)	20 (64.5)			
<b>Bleeding</b>					
Yes	03 (75.0)	01 (25.0)	1.905	1	0.07*
No	12 (38.7)	19 (61.3)			
<b>Hyperleucocytosis</b>					
Yes	04 (100.0)	00 (00.0)	4.227	1	0.04*
No	11 (35.5)	20 (64.5)			

DF=degree of freedom; \*Fisher's exact test.

**Table 3: Factors independently associated with in-hospital mortality.**

Variables	B	S. E.	OR (95% CI)	P value
<b>Metastasis</b>	1.253	0.762	3.500 (0.786-15.578)	0.10
<b>Shock</b>	-3.470	0.757	0.031 (0.0007-0.137)	<0.001
<b>Acute kidney injury</b>	-1.186	0.947	0.306 (0.048-1.954)	0.21
<b>Multi-organ failure</b>	-1.671	0.883	0.188 (0.33-1.060)	0.04
<b>Hyperleucocytosis</b>	1.520	0.762	4.571 (1.027-20.347)	0.04

B=unstandardized beta; S. E=standard error; OR=odds ratio; CI=confidence interval.

**Factors associated with loss to follow up of survivors**

The only factor that was significantly associated with loss to follow up in this study was residence outside the study location (p=0.03) and it remained an independent predictor (p=0.04) of loss to follow up when subjected to binary logistic regression analysis. Age group category (p=0.09), gender (p=0.70), social status (p=0.40), long hospital stay during the initial treatment (p=0.53), tumour type (p=0.31), metastatic disease (p=0.35), tumour remission (p=0.20) were found not to be significantly associated with loss to follow up visits among survivors.

**DISCUSSION**

This study has demonstrated the predominance of malignant tumours among children under-five years of age, male subjects, solid tumours and the occurrence of high in-hospital mortality with a greater percentage of survivors being lost to follow up. The finding of solid tumours as the commonest malignancies in this study is in consonance with reports from other studies and has been linked to embryonal tumours occurring mostly in early childhood, predominantly among children under-five, which were the major age group category in this

study.<sup>10,11,14,15,22</sup> Male preponderance in this study is also comparable to reports from previous studies conducted in Nigeria and is thought to be as a result of cultural factors as more males than females often benefit from medical attention in our setting.<sup>9-12,14,15,24</sup>

The occurrence of high in-hospital mortality in this study is comparable to reports from other studies conducted in Nigeria, some parts of Africa and South America.<sup>9-16,22</sup> Like in these studies, majority of the subjects in our study presented late, with most (82.9%) of them presenting after a month to more than 3 months of occurrence of the first noticeable symptom and 68.6% having metastatic disease at presentation. In well-resourced countries, a good number of children less than 15 years of age are said to commence treatment less than a month from the onset of symptoms.<sup>25</sup> Financial difficulties associated with poverty and non-availability of health insurance, lack of awareness and belief for spiritual causes of illness by caregivers and delayed referral of patients to centers where appropriate management can be provided have been attributed to late presentation in resource constraint settings like ours.<sup>9-11</sup> Moreover, the socio-economic status of the caregivers of the subjects in our study was largely (71.4%) low and could influence the health

awareness and health seeking behaviour of these caregivers. Socio-economic status has been documented as an important determining factor associated with the outcome of cancer management, with low socio-economic status increasing the risk of mortality in patients with malignancy.<sup>26</sup>

The long health service delay in diagnosis, lack of/difficulty in accessing appropriate treatment and supportive care services such as cytotoxic drugs, blood and blood products as well as the absence of clinical trial protocols are said to be some of the challenges increasing the risk of mortality in cancer patients.<sup>8-11</sup> The absence of an oncology unit, clinical paediatric oncologists, nurses and other healthcare providers dedicated to the care of the studied subjects could also have interfered with the delivery of quality care to the subjects, thereby serving as a contributing factor to the high in-hospital mortality in this study. A designated paediatric oncology ward and multi-disciplinary team care has been found to improve the outcome of cancer cases, but as in this study, these requirements are grossly deficient in some parts of Nigeria.<sup>8</sup>

The independent predictors of in-hospital mortality among the subjects in this study were shock, multi-organ failure and hyperleucocytosis. These are oncologic emergencies requiring prompt identification and preferably, management in the ICU setting in order to reduce mortality. Although the ICU management option was offered to the caregivers, they could not afford the payment as they were most likely exhausted from the out of pocket payment of fees in the course of in-hospital and other related demands. Unwillingness on the part of some parents or caregivers to continue spending indefinitely after prolonged stay in the hospital, coupled with no remarkable clinical changes, especially in those who presented with advanced stages of the disease has been reported as a challenge in patient management.<sup>15</sup>

In contrast to reports from other studies, the type of tumour, socio-demographic factors such as age, gender, socio-economic status and complications like bleeding, sepsis or malnutrition were not associated with in-hospital mortality in this study.<sup>9,27,28</sup> Sociodemographic factors not predicting mortality in our study could be related to the fact that caregivers were mainly similar in terms of social status, with the majority of children having similar characteristics in terms of gender and age group category. The observed differences were therefore not significant enough to affect the mortality pattern in this study. Malnutrition and sepsis are usual occurrences among children in our setting and the expertise in terms of treatment and monitoring has improved over time. Applying similar management strategies in the treatment of subjects that had co-morbidities of malnutrition or sepsis might have contributed to successful treatment and a reduction of the risk of sepsis or malnutrition related mortality in the subjects.

The high rate of loss to follow up in this study is in consonance with reports from other studies.<sup>9,11,12,14,15,22</sup> In our study, subjects from locations distant from the study location were more likely to default from follow up visits. This finding is consistent with those of reports from Zambia and India.<sup>22,29</sup> In the Zambian study, proximity to the treatment center from home was associated with decreased risk of treatment abandonment. Two-thirds of their cohorts resided in provinces over 300 km from the study location and this led to the high rate of default from treatment.<sup>22</sup> The study of retinoblastoma patients in India found that abandonment of treatment was more common in patients from rural areas, distant from the study location.<sup>29</sup> Keeping patients in our facility for the required duration of treatment is not feasible, affordable or bearable by the caregivers. They are often discharged to be re-admitted few days before the subsequent course of treatment. Despite pre-treatment counselling, caregivers for some reasons still default follow-up visits when allowed home. A lot of motivation is needed to encourage caregivers not to abandon treatment as this action is almost certain to increase the risk of mortality of children with cancers. Abandonment of treatment was a significant cause of treatment failure in the study conducted in Zambia.<sup>22</sup>

Our study being prospective in nature provided us with the opportunity of obtaining adequate information on most medical details of the subjects. The sample size could, however, be a tip of an iceberg as many children with malignancies in our setting especially in the earlier stages of the disease are likely to remain undiagnosed or resort to alternative treatment measures without presenting to tertiary health facilities like UDUTH, Sokoto. Our study did not assess the healthcare provider factors such as patient-health worker relationship, service delivery or health facility environmental factors which if not appropriate, could also have explained the high rate of subjects default from follow up visits.

## CONCLUSION

The high in-hospital mortality and loss to follow-up in this study is worrisome. It is obvious that more attention needs to be paid to increasing the awareness of the population in the study location by way of health education on childhood cancers and the implication of late presentation as well as default from follow up visits. Mortality can be reduced by prompt identification and management of oncologic emergencies preferably in the ICU setting, the availability of a team of paediatricians and other health workers dedicated to a focused approach in the management of childhood cancers in the study location and the availability of support services as well as social insurance schemes to buttress the financial hardships faced by the caregivers of children suffering from malignancies.

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