

# PREDICTORS OF TREATMENT OUTCOMES IN ENDEMIC BURKITT'S LYMPHOMA PATIENTS AT JARAMOGI OGINGA Odinga TEACHING AND REFERRAL HOSPITAL, KISUMU COUNTY, KENYA

Lamek Onyango (lameckowuor@gmail.com)<sup>1,3</sup>, Dr. Amolo Asito, PhD (jakogwanjo@gmail.com)<sup>2</sup>

<sup>1</sup>Department of Molecular Biology Application Specialist, Bio-Zeq Kenya Limited

<sup>2</sup>Department of Biological Sciences, School of Biological and Physical Sciences

Jaramogi Oginga Odinga University of Science and Technology, Kenya

<sup>3</sup>School of Health Sciences, Jaramogi Oginga Odinga University of Science and Technology

**Abstract-** Endemic Burkitt's lymphoma is the most common childhood cancer in equatorial Africa, where it is about ten times more common than in Europe. It also is the most prevalent pediatric malignancy among children in Western Kenya. Although it is highly responsive to chemotherapy, the number of its mortality cases associated with it is still high and the underlying reasons for this high mortality rates is still unknown. Therefore, this study describes the demographical and clinical characteristics of eBL patients observed over time and determines the influence of these characteristics on eBL patient treatment outcome at JaramogiOgingaOdinga Teaching and Referral Hospital (JOOTRH). This was a retrospective study design intended to describe the clinical and demographical characteristic and their influence on the treatment outcome of eBL patients. A total of 178 eBL children (103 boys and 75 girls, with a mean age of 7.37 years) who were diagnosed between 2009 and 2014 were enrolled in the study. There was no significant difference in the proportion of boys and girls, and the mean age (7.37 years) at diagnosis remained similar throughout the study period. Those presenting with abdominal tumor only were 72 (40.40%) while those with facial tumor only were 28 (15.70%). Children presenting with a combination of abdominal and facial tumor were 23 (12.90%). HIV positivity was 3.9 %, and did not differ between different periods. A total of 125 (70.2%) children received induction chemotherapy phase and they had no significant difference in proportion throughout the study period. In addition 108 (60.7%) of the children received consolidation phase of chemotherapy while only 35 (19.7%) received maintenance phase of chemotherapy. In terms of eBL patients response to chemotherapy, 49 (27.5%) did not respond, 59 (33.2%) had complete remission, 33 (18.5%) had partial remission, 31 (15.0%) had stable disease, while 18 (5.0%) had relapse. But there were no changes in the proportions in response to chemotherapy. Hematological indices revealed that 46 (26.1%) had severe anemia, 110 (62.5%) had mild anemia while only 20 (11.4%) had normal anemia levels. A total of 62 (34.83%) children died during the follow up; analysis also revealed that 13 of the children who received all phases of consolidation chemotherapy died while 6 died despite receiving maintenance chemotherapy. There was no significant difference in mortality rates in children with symptoms of fever (p=0.095),

weight loss (p=0.403), night sweats (p=0.165), severe infection (p=0.774) and malaria (p=0.343). Children presenting with testicular tumour (HR 31.77, 95% C.I 3.28-307.62, p=0.003) and lung parenchymal tumour (HR 8.65, 95% C.I 2.00-37.24, p=0.004) had increased mortality rate relative to those presenting with other tumors. There was no statistical difference in the children mortality rate by HIV status (HR 1.37, 95% C.I 0.60-3.13, p=0.455). Further analysis revealed that those with severe anemia had increased mortality rate (HR 2.07, 95% C.I 3.67-0.97, p=0.012). Endemic Burkitt's lymphoma is more prevalent among male children at the age of 5-9 years. Patients who completed the entire treatment cycle up to maintenance therapy had low mortality rate. However, patients who presented with lung parenchyma, testicular tumor, and those who had severe anemia had higher mortality rate. The results of this study indicated that the sensitivity and specificity of the techniques used for BL diagnosis needed to be validated since our studies reveal that children diagnosed using histology had significantly lower mortality rate relative to those who were diagnosed through cytology. This study is helpful in deciding on the feasible therapy and support care system for improving therapeutic strategies and in designing future clinical trials.

**Index Terms-** Cancer, Patients, Burkitt's, Lymphoma, Malignancy, Endemic.

## I. INTRODUCTION

Estimates are that, by 2020, cancer will become the world's single leading cause of death and already cancer mortality has eclipsed the total number of deaths attributable to HIV/AIDS, tuberculosis, and malaria combined (WHO, 2011; Ferlay *et al.*, 2011). Furthermore, the World Health Organization (WHO) projects that by 2020, there will be 16 million new cancer cases and 27 million cases by 2030; 70% of these will be in developing nations, and an excess of 1 million will occur in sub-Saharan Africa alone, which is further compounded by the advancing acquired immunodeficiency syndrome (AIDS) epidemic (Mwanda *et al.*, 2009).

There are scant resources in this part of the world to diagnose, treat and support cancer patients through chemo-

radio- and surgical therapy resulting in unacceptably high treatment-related mortality rates, median survival rates on the order of several weeks, and very limited data on how patient demographic and clinical parameters at time of diagnosis influence patient outcomes. Inadequate trained manpower to address this emergent crisis is a most significant challenge for cancer control in Africa (Sissolaket *et al.*, 2007; UNAIDS, 2011).

One of the most common Non-Hodgkin's lymphoma in Africa is Endemic Burkitt's lymphoma (eBL), which is a pediatric malignancy (Ogwanget *et al.*, 2008). This malignancy has high incidence in areas that experience stable *Plasmodium falciparum* (*P. falciparum*) transmission, and both Epstein-Barr virus infection (EBV) and holoendemic *P. falciparum* are etiologically linked to this B cell neoplasm (Rochford *et al.*, 2005; Mwandaet *et al.*, 2009). In addition, histopathological studies and diagnosis of cases of BL have revealed that there are three different clinical variants that differ in their geographical distribution and incidences in different populations (Mbulaitey *et al.*, 2010). These three variants include the eBL, common in Africa especially in malaria endemic regions of sub-Saharan Africa and has a high incidence (Ogwanget *et al.*, 2008), the sporadic BL with low incidence mainly common in developed countries and northern Africa, and AIDS associated BL which has been associated with rise in HIV infection (Orem *et al.*, 2009). Moreover, eBL present as jaw or orbital (facial) tumors while sporadic BL mainly present as abdominal tumors or tumors with bone marrow involvement (Ogwanget *et al.*, 2008).

Burkitt's lymphoma (BL) is an aggressive extra nodal B cell lymphoma that can present in a number of different sites including jaw, abdomen, central nervous system, thyroid gland, orbital, and breast or a combination of these areas (Mwandaet *et al.*, 2004; Ogwanget *et al.*, 2008). It may also present as generalized lymphadenopathy, testicular tumor, renal mass, bone involvement, thoracic involvement, lung parenchymal involvement, mediastinal tumor or pleural disease including effusion (Orem *et al.*, 2011). However, jaw and abdominal tumors are the most common sites of presentation (Mwandaet *et al.*, 2004). Interestingly, there are different epidemiologic patterns associated with children presenting with jaw compared to abdominal tumors. For example, while the median age of onset is 6 to 7 years for BL (Rainey *et al.*, 2007; Carpenter *et al.*, 2008), jaw tumors are associated with a younger age of presentation and more frequently found in males, while abdominal tumors are common in older children, and there is a more equal distribution among males and females (Ogwanget *et al.*, 2008). A study in Uganda revealed that a third of female cancer patients present with ovarian mass and that there is an increase in patients presenting with hepatic mass and malignant pleocytosis (Orem *et al.*, 2011). Despite the fact that eBL has several distinct demographic and clinical pictures most studies have looked at it as a single clinical entity (Asitoet *et al.*, 2010). There is still a paucity of data in the demographic characteristics of patients presenting with BL patients at the JaramogiOgingaOdinga Teaching and Referral Hospital (JOOTRH) which is the main referral hospital for cancer patients offering chemotherapeutic treatment for eBL in the western Kenya region (Asitoet *et al.*, 2010).

Evidence suggests that demographic and clinical characteristics at the time of diagnosis are predictors of treatment

outcomes in BL patients (Mwandaet *et al.*, 2009; Orem *et al.*, 2011; Bateganyaet *et al.*, 2011). A study in in AIDS related non-Hodgkin's lymphoma revealed that serum lactate dehydrogenase (LDH), hemoglobin levels, and access to antiretroviral therapy were predictors of overall survival (Mwandaet *et al.*, 2009). Similarly, a study in Uganda found that while treatment response rates were similar regardless of HIV serostatus, median survival in HIV-infected children was less than HIV-negative in determinate children (Orem *et al.*, 2009). However, this study did not indicate the type of chemotherapy administered to these children. Another study in BL patients in Uganda revealed that, age, site of tumor presentation, HIV status, increased cycles of chemotherapy and symptoms such as fever, weight loss, night sweats, anemia, severe or recurrent malaria are predictors of treatment outcomes (Orem *et al.*, 2011). Several reports have clearly identified the challenges in administering dose-intense chemotherapy to children with eBL in sub-Saharan Africa relative to European countries (Mwandaet *et al.*, 2002; Hesselinget *et al.*, 2003; Hesselinget *et al.*, 2008). In addition, a Ugandan study reported that the median survival of those patients presenting with non-Hodgkin's lymphoma in whom mortality status was confirmed as 2 months; of these 32% were HIV-seropositive; and median survival among patients with HIV infection receiving antiretroviral therapy was comparable to those without HIV infection (Bateganyaet *et al.*, 2011).

The main objective was to determine clinical characteristics and predictors of treatment outcomes in eBL patients at JaramogiOgingaOdinga Teaching and Referral Hospital.

The justification of the study is that demographic and clinical characteristics are important predictors of treatment outcomes in BL patients (Orem *et al.*, 2009; Orem *et al.*, 2011; Molyneux *et al.*, 2014). For example, abdominal tumors, anemia other hemotological parameters, age and HIV status are associated with poor treatment outcomes (Mwanda *et al.*, 2009; Orem *et al.*, 2009; Orem *et al.*, 2011). Moreover, studies have shown that HIV-infected individuals are at increased risk of AIDS related BL (Mwandaet *et al.*, 2009; Rodrigo *et al.*, 2012). This has created enormous challenges to national public health programs for prevention, diagnosis and treatment of this tumor (Orem *et al.*, 2009; Mwandaet *et al.*, 2009). Of significance are studies showing that there is a lot of heterogeneity in BL in terms of demographic and clinical characteristics (Ogwanget *et al.*, 2008; Asito *et al.*, 2010). A study in Malawi showed that BL patient's response to therapy correlates with the expression of EBV lytic related genes (Labrequeet *et al.*, 1999).

## II. LITERATURE REVIEW

### Epidemiology of Burkitt's lymphoma

Endemic Burkitt's lymphoma is the most common childhood cancer in equatorial Africa, where it is about ten times more common than in Europe. The incidence is higher in areas with high rates of malaria. In Kenya, the highest rates are seen in Western region and the Coastal region. The country prevalence stand at 0.61 per 100 000 children, while in Nyanza province it is 2.15 cases/100 000 children/year ( Ogra Foundation, 2012).

BL is an aggressive B-cell non-Hodgkin's lymphoma with several epidemiological subtypes: endemic Burkitt's lymphoma

(eBL) prevalent among children in equatorial Africa, sporadic BL prevalent among adolescents in western countries, Acquired Immunodeficiency Syndrome (AIDS)-related BL, common in 30% of individuals infected with human immunodeficiency virus (HIV) and pleomorphic or atypical variants (Orem *et al.*, 2011; Mbulaiteye *et al.*, 2011). Although all these variants are pathologically indistinguishable with histopathologically showing that they present as poorly differentiated lymphoma with cells showing little variation in size and shape and exhibiting a starry sky appearance (Rochford *et al.*, 2005; Mbulaiteye *et al.*, 2011), they all exhibit *c-my* chromosomal translocation (Wilmore *et al.*, 2015). In addition, BL show a lot of heterogeneity in terms of geographical distribution, gender distribution, clinical presentation and age of occurrence (Klein *et al.*, 1995; Rochford *et al.*, 2005).

Earlier studies have shown that in sub-Saharan Africa, eBL is the most common pediatric malignancy associated with a lot of morbidity and mortality (Ogwanget *et al.*, 2008; Mwanda *et al.*, 2009; Orem *et al.*, 2011). This tumor has an average annual incidence of 2 per 100,000 children, with a peak age range of 5 to 9 years (Mwanda *et al.*, 2004; Parkin *et al.*, 2008). In 1964, Epstein-Barr virus (EBV) was discovered in a tumor sample obtained from a patient with eBL indicating that EBV was one of the etiological agent involved virus-mediated oncogenic processes (Thorley-Lawson *et al.*, 2008). Endemic BL is most common in children residing in areas with the highest malaria transmission intensities (Rainey *et al.*, 2007). Studies have shown this pediatric malignancy is common in malaria endemic regions of sub-Saharan Africa, Papua New Guinea and South America (Rochford *et al.*, 2005).

In Kenya there is geographical overlap between the incidence of eBL with endemic malaria transmission with coastal and Western regions having the highest incidences (Mwanda *et al.*, 2004). A study in western Kenya revealed that even in areas with high incidence of eBL there are spatial distribution with some regions presenting as eBL hot spots (having high incidence) while other were cold spots (low incidence) (Rainey *et al.*, 2007). Significantly, this region has the highest prevalence of HIV in Kenya (NASCOP, 2014) and studies have shown that it has an increment of AIDS related non-Hodgkin's lymphomas (Mwanda *et al.*, 2009; Orem *et al.*, 2011).

#### **Demographic and clinical characteristics of eBL patients**

Endemic Burkitt's lymphoma (eBL) is an invasive B-cell lymphoma that shows predilections for the jaw, abdominal, central nervous system, thyroid glands, orbital areas and the breast or a combination of these areas (Magrath, 1997; Bishop *et al.*, 2000). It can also present as lymphadenopathy, testicular tumor, renal mass, bone involvement, thoracic involvement, lung parenchymal involvement, mediastinal tumor or pleural disease including effusion (Orem *et al.*, 2011). In addition females may also present with ovarian mass (Orem *et al.*, 2011). Although jaw and abdominal tumors are the most common sites of presentation in BL patients, studies have shown that lymphadenopathy and thoracic involvements are common in BL cases with HIV (Ogwanget *et al.*, 2008; Mwanda *et al.*, 2009; Orem *et al.*, 2011). Interestingly, those with jaw tumors are mostly males and relatively younger than those presenting with abdominal tumors who are mostly females (Rainey *et al.*, 2007; Carpenter *et al.*,

2008; Ogwanget *et al.*, 2008). Although these studies indicate that there is a variation in demographic characteristics of BL patients there is a paucity of data on the demographic characteristics of patients presenting with BL patients at the JOOTRH the main referral hospital for cancer patients offering chemotherapeutic treatment for BL in the western Kenya (Asito *et al.*, 2010). Therefore, this study evaluated the demographic characteristics of patients presenting with BL by HIV status.

Apart from demographic characteristics, BL patients also present with symptoms such as fever, weight loss, night sweats, anemia, severe or recurrent malaria (Bategaya *et al.*, 2011; Orem *et al.*, 2011). They also present with higher levels of LDH especially those with advanced stage tumors or HIV infection (Mwanda *et al.*, 2009; Miles *et al.*, 2012). In addition they also present with high EBV viral loads associated with heavy tumor burden (Asito *et al.*, 2010). The other clinical hallmark of BL is hematological perturbation that results in organ failures (Olowu *et al.*, 2006; Mwanda *et al.*, 2009). Earlier study has shown that the severity of hematological perturbation is associated with tumor burden (Katodritou *et al.*, 2009). Severe anemia is the most common hematological complication in BL patients associated with tumor metastasis (Bhattathiri, 2001; Mittelman *et al.*, 2003; Birgegard *et al.*, 2006) and the severity of anemia is prognostic risk factor for the patient's survival (Birgegard *et al.*, 2006; Katodritou *et al.*, 2009). The other clinical characteristics associated with BL include splenomegaly and hepatomegaly (Mwanda *et al.*, 2005; Bategaya *et al.*, 2011). Although discrepancy in the incidences and the prognostic influence of pre-chemotherapy anemia in lymphoma patients have been reported in developed countries (Birgegard *et al.*, 2006; Teuffe *et al.*, 2008), there is a paucity of data on the incidences of anemia in BL patients and their prognostic influence on patient outcomes in sub-Saharan Africa. Significantly, clinical features of BL show geographical variation (Mwanda *et al.*, 2005) indicating that the clinical characteristics vary by regions. This is further compounded by the fact that viremia in advanced HIV disease status result in more severe hematological perturbations (Otieno *et al.*, 2006; Dikshit *et al.*, 2009). Thus, due to rapid rise of HIV and AIDS related BL in Kenya (Mwanda *et al.*, 2009), there is need to evaluate the clinical characteristics of children presenting with BL at JOOTRH. Earlier studies have shown that both the demographic and clinical characteristics of BL patients impact on patient treatment outcomes (Mwanda *et al.*, 2009; Orem *et al.*, 2011). Hence there is need for understanding how these factors may impact on treatment outcomes of BL patients in an area with high BL incidence rates and HIV prevalence (Rainey *et al.*, 2007; NASCOP, 2014).

#### **Predictors of treatment outcomes in BL patients**

Burkitt's lymphoma is an aggressive tumor with rapid doubling time. It is easily recognizable and potentially responsive to chemotherapy (Meremikwue *et al.*, 2005; Orem *et al.*, 2011; Molyneux *et al.*, 2014). However, treatment outcome of BL in sub-Saharan Africa remains poor partly due to socioeconomic factors such as poverty that hinder access to specialized health care and lack of early diagnosis due to poor health infrastructure (Mwanda *et al.*, 2009; Orem *et al.*, 2011; Molyneux *et al.*, 2014). Treatment outcomes are generally

categorized as complete remission where there is no evidence of disease, partial remission where there is 50% or greater decrease in tumor size, stable disease where there is neither decrease nor increase in disease, no response where there is progressive disease with new disease appearance despite chemotherapy, or recurrent disease with appearance of tumor following documentation of remission (Orem *et al.*, 2011; Molyneux *et al.*, 2014). Previous studies on treatment outcomes have been stratified into event-free survival (EFS) and overall survival (OS) (Mwanda *et al.*, 2009). Moreover, several studies have demonstrated that both demographic and clinical factors may serve as prognostic factors for treatment outcomes in BL patients (Orem *et al.*, 2011).

Although the types of regimen, dose and schedule of chemotherapy for BL in Kenya is similar to that of developed countries, the prognosis for BL cases in Kenya are relatively low compared to Europe and United States (90%) (OGRA Foundation, 2012). This is comparable to survival rates reported in other equatorial African countries (Buckle, *et al.*, 2013). These

data therefore suggest that there may be context specific clinical characteristic issues affecting response to chemotherapy. Interestingly, an earlier study revealed that there is geographical variation in clinical characteristics of BL patients in Kenya (Mwanda *et al.*, 2005). These data indicate a need for understanding of prognostic markers of patient survival following chemotherapy in western Kenya with high BL incidence (Asito *et al.*, 2010; Rainey *et al.*, 2007). This will ultimately lead to improving patient management and treatment leading to positive treatment outcomes.

**Conceptual framework**

In the current study, a good prognosis or treatment outcomes is influenced by demographic, clinical factors, access to chemotherapy and antiretroviral therapy. It is appreciable that all elements of access to chemotherapy should be considered comprehensively and how they influence treatment outcomes in BL patients.

These factors have been summarized in Figure 2.1.

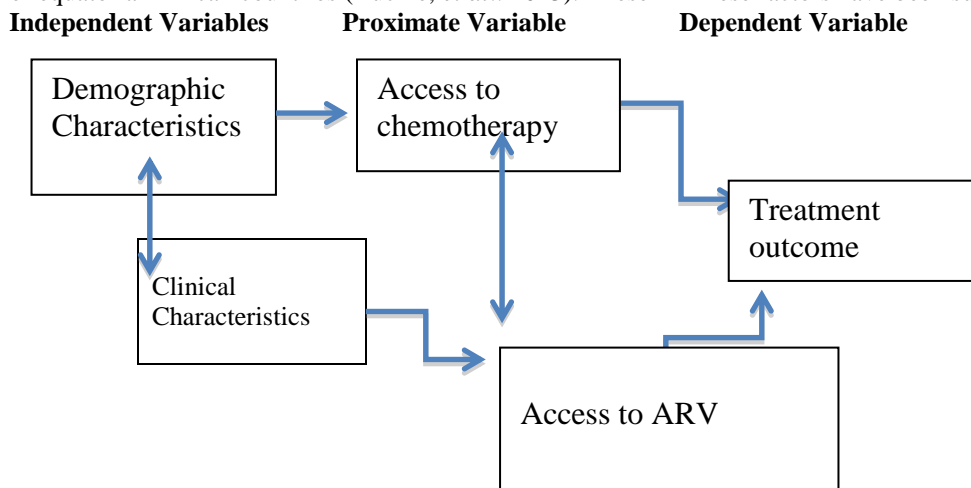


Figure 2. Conceptual framework, Associative conceptual diagram (Starfield, 2002) adopted with modifications

**III. RESEARCH METHODOLOGY**

**Study location**

JaramogiOgingaOdinga teaching and referral hospital (JOOTRH) (Appendix 1) is a public regional referral hospital, which serves as the referral center for children diagnosed with cancer in western Kenya (Buckle *et al.*, 2016). It is located in an urban setting in Kisumu City with coordinates of 005°20'N34046'17"E Kenya; the third largest city in the country (CNES, 2015). It has an oncology and palliative care unit, with ward five assigned to be the pediatric oncology ward and acts as the main pediatric cancer diagnostic and management center in western Kenya (Asito *et al.*, 2011). The hospital is also located in a region with one of the highest incidence of eBL in Kenya (Mwanda *et al.*, 2004; Rainey *et al.*, 2007). It serves an area with one of the highest HIV prevalence (18.7%) in Kenya (NASCOP, 2014).

**Study design**

This study used a retrospective study design. It specifically intended to describe the clinical and demographical characteristic and their influence on the predictors of treatment outcome of

eBL patients managed overtime at JaramogiOgingaOdinga Teaching and Referral Hospital (JOOTRH).

**Data Collection**

Medical records for BL patients available at JOOTRH from 2009 to 2014 was retrieved and reviewed for demographic and clinical characteristics. eBL patients information on sex, age, diagnosis technique (clinical diagnosis, cytology or histology), clinical symptoms, tumor presentations, HIV status, haemoglobin levels, chemotherapy cycle, treatment complications and response to chemotherapy was abstracted using standardized data abstraction form (Appendix 2). The abstraction form was developed with adequate procedural manual to ensure reliability, accuracy and consistency of information. Patients were considered lost to follow-up if they were referred to other facilities.

Tumor diagnosis: Local Licensed pathologist conducted the clinical examination and requested for either fine-needle aspiration (FNA) or Biopsy for BL diagnosis confirmation. They reviewed the laboratory results and provided the diagnostic information that was based on their observation. Trained medical laboratory personnel prepared the specimen and performed the lab test for examination. Cytology and histology techniques are

the two laboratory procedures that were used for confirming BL in the FNA and Biopsy specimens collected the pathologist at JOOTRH.

Plain radiography and ultrasound were used to determine the tumor presentation sites. Abdominal ultra sound was used to test for abdominal involvement while chest X-ray was used to investigate mediastinal involvement and to rule out tuberculosis. Lumbar puncture procedure was used to collect cerebral spinal fluid for cytological test for cerebral involvement before giving the first dose of intrathecal chemotherapy. In addition, before the start of chemotherapy treatment, blood smear for malaria test, HIV test, urine and stool microscopy test was performed. Finally, to qualify the patient fit for chemotherapy; kidney test, liver test and complete blood count were done.

The data was cleaned, edited and coded to avoid incompleteness during entry. Data on the characteristics of children with BL was summarized by means and standard deviations, or with proportions; differences in proportions and means was tested by the chi square test, t-test, z-test or ANOVA procedures where necessary. For analysis of predictors of treatment outcome, the temporal scale was determined as from the time of BL diagnosed, while death due to BL was considered to be a failure status. All other means of leaving the study were considered to censor the observed survival. The Cox proportional hazards model was fitted to estimate the hazard ratio (HR), reflecting the effect of the covariates on survival. In addition, likelihood ratio test was used to adjust the HR for both age and sex. Data analysis was performed using STATA software version 16.

#### IV. RESULT

##### Demographic characteristics of the study population

As shown in table 4.1, a total 178 patients aged 0-17 years [103 (57.9%) boys and 75 (42.1%) girls] fulfilled the inclusive criteria for the study and were involved in the consequent analysis. The mean age at diagnosis and first admission at JOOTRH was 7.37 years (SD 3.29). Most children 48.3% were aged between 5 and 9 years at BL diagnosis. There was no significant difference in the proportion of boys and girls, and the mean age at diagnosis remained similar throughout the study period.

##### Clinical characteristics of the study population

As shown in table 4.2, majority of the children 158 (88.8%) had clinical diagnosis of BL, with 81.5% having cytological confirmation of the disease and only 7.3% having histological confirmation. The proportion for BL confirmation over the study period had increased to 89.5% for cytological technique while none of the patients received histological procedure in the last two years of the study. The most common symptoms at diagnosis were fever, night sweats, weight loss, severe infection, anemia and malaria. However, the proportion of children presenting with fever remained similar throughout the study period as well as the proportion of children presenting with anemia, night sweats and severe infection.

##### Results:

A total of 125 (70.2%) children received induction phase of chemotherapy but there was no significant difference in proportion throughout the study period ( $p=0.25$ ). In addition 108

(60.7%) of the children received consolidation phase of chemotherapy while only 35 (19.7%) received maintenance phase of chemotherapy. Although the proportion of children receiving both induction and consolidation phases of chemotherapy remained similar throughout the study period there was a significant reduction in children receiving maintenance phase of chemotherapy over the study period ( $p<0.0001$ ). The children presented with various forms of complications following chemotherapy (Table 4.4). All children suffering from fall of hair and vomiting, 47 (26.4%) from diarrhea, 45 (25.3%) suffering from pain, 67 (37.6%) suffering from headache, 51 (28.6%) from stomach pain, 25 (14%) from back pain, 2 (1.1%) from shivers, 3 (1.7%) from itching and 7 (3.9%) from constipation. The proportion of treatment complication remained the same during the study period. However, there existed a significant decrease in the proportion of pain over the study period ( $p=0.035$ ).

There was no significant difference in mortality rates in children with symptoms fever, anemia, weight loss, night sweats, severe infection and malaria. Table 4.8 shows the combination of facial and abdominal tumor had no statistical significance association with mortality rate (HR 0.77, 95% C.I 0.48-0.90,  $p=0.285$ ). Children presenting with testicular tumor (HR 31.77, 95% C.I 3.28-307.62,  $p=0.003$ ) and lung parenchymal tumor (HR 8.65, 95% C.I 2.00-37.24,  $p=0.004$ ) had increased mortality rate relative to those presenting with other tumor types. Further analysis revealed that those with severe anemia ( $\leq 8$  g/dL) had increased mortality rate (HR 2.07, 95% C.I 1.17-3.67,  $p=0.012$ ).

Children with information on chemotherapy, 26 died despite receiving induction chemotherapy while 31 died without receiving induction chemotherapy. Analysis also revealed that 13 of the children who received all phases of consolidation chemotherapy died while 43 of the children died without receiving consolidated chemotherapy. For those who received maintenance chemotherapy there were 6 deaths, similarly among those who did not receive maintenance chemotherapy.

An increase in mortality rate in children who had no record of receiving induction chemotherapy (HR 4.1, 95% C.I 1.75-9.59,  $p=0.001$ ) and those who did not receive induction therapy (HR 2.34, 95% C.I 1.57-3.57,  $p<0.0001$ ) relative to those who received all phases of induction chemotherapy. Similarly there was an increased mortality among children who had no record of receiving consolidation chemotherapy (HR 5.2 95% C.I 2.20-12.29,  $p<0.0001$ ) and those who did not receive any consolidation chemotherapy (HR 2.97, 95% C.I 2.07-4.27,  $p<0.0001$ ) relative to those who received all phases of consolidation chemotherapy. An increased mortality rate was also revealed in children who had no records of receiving maintenance chemotherapy (HR 2.38, 95% C.I 1.52-3.72,  $p<0.0001$ ), those who received none (HR 8.84, 95% C.I 3.71-21.07,  $p<0.001$ ) and those who did not complete maintenance chemotherapy cycle (HR 5.16, 95 CI 3.20-8.33,  $p<0.001$ ).

Children who achieved complete remission after chemotherapy had lower mortality rate (HR 0.58, 95% C.I 0.42-0.81,  $p=0.001$ ) while those that had no response to chemotherapy had an increased mortality rate (HR 2.91, 95% C.I 2.00-4.23,  $p<0.0001$ ).

**Table 4.** Predictors of treatment outcome of Burkitt's lymphoma diagnosed patients aged <18 years at JaramogiOgingaOdinga Teaching and Referral Hospital by period of diagnosis

	Alive (n=92) (51.69%)	Deceased (n=62) (34.83%)	Referred (n=24) (13.48%)	HR (crude)	95% CI	<sup>a</sup> P-value	HR (adjusted for sex and age)	95% CI	<sup>b</sup> P-value
<b>Treatment Complication</b>									
Diarhoea	22(23.9)	21(33.9)	4(16.7)	1.14	0.81-1.61	0.449	1.13	0.78-1.63	0.504
Vomit	92(100)	62(100)	24(100)	1	-	-	1	-	-
Fall of hair	92(100)	62(100)	24(100)	1	-	-	1	-	-
Pain	19(20.7)	20(32.3)	6(25)	0.93	0.66-1.32	0.691	0.97	0.68-1.38	0.849
Headache	40(43.5)	19(30.6)	8(33.3)	0.7	0.51-0.96	0.025	0.7	0.50-0.97	0.033
Stomach pain	34(37)	12(19.4)	5(20.8)	0.96	0.69-1.34	0.811	0.94	0.67-1.31	0.701
Back pain	16(17.4)	6(9.7)	3(12.5)	0.89	0.58-1.37	0.593	0.81	0.52-1.28	0.371
Shever	1(1.1)	0	1(4.2)	1	0.25-4.04	1	1.03	0.25-4.24	0.964
Itching	1(1.1)	2(3.2)	0	0.84	0.27-2.64	0.761	0.82	0.25-2.64	0.741
Constipate	2(2.2)	4(6.5)	1(4.2)	1.64	0.76-3.51	0.205	1.73	0.73-4.09	0.211
<b>Chemotherapy Response</b>									
Relapse	8(8)	7(11.3)	3(12.0)	0.92	0.55-1.52	0.735	0.89	0.53-1.49	0.648
Stable Disease	3(3.3)	12(19.4)	2(8.3)	1.31	0.67-1.91	0.635	1.13	0.67-1.91	0.647
No response	0	36(58.1)	13(54.2)	2.48	1.76-3.47	<0.001	2.91	2.00-4.23	<0.001
Complete remission	56(62)	2(3.2)	0	0.62	0.45-0.86	0.004	0.58	0.42-0.81	0.001
Partial remission	24(26.1)	4(6.5)	5(20.8)	0.77	0.52-1.13	0.181	0.8	0.54-1.20	0.287

Data are number (%), unless otherwise indicated. <sup>a</sup>P-value refers to crude HR obtained using Cox model. <sup>b</sup>P-value refers to HR adjusted for both sex and age obtained using Cox model and likelihood-ratio test (except for the analysis of testicular cancer or, sex and age themselves, where sex and testicular cancer were adjusted for age, and age was adjusted for sex)

## V. DISCUSSION

This study reveals that the peak incidence of eBL is between the age of 5-9 year with a predominance of males. This is consistent with previous findings in East Africa (Ogwang *et al.*, 2008; Orem *et al.*, 2011). Of significance, earlier studies in Kenya indicated that there is geographical variation in clinical presentation of eBL (Otieno *et al.*, 2001; Mwanda *et al.*, 2004). In line with these findings this study found that a majority of patients presented with facial and abdominal tumors indicating that clinical characteristics of BL has remained unchanged over a long period of time (Mwanda *et al.*, 2004; Orem *et al.*, 2011; Aka *et al.*, 2012). However, as opposed to a previous study in Uganda that found more children presenting with facial tumors relative to abdominal tumors (Orem *et al.*, 2011), this study found that there were more children presenting with abdominal tumors relative to facial in line with a study in Tanzania (Aka *et al.*, 2012). This disparity in clinical presentation can partly be due to the reported changes in BL tumor presentation in Africa (Otieno *et al.*, 2001; Oguonu *et al.*, 2002; Mwanda *et al.*, 2004; Sherif *et al.*, 2015).

Although this geographical variations in tumor presentation can be attributed to random variations, several studies from diverse regions in Africa and all over the world indicates that most BL patients present with abdominal tumors (Naresh *et al.*, 2004; Temmim *et al.*, 2004; Sherief *et al.*, 2015), further indicating that apart from changes in tumor presentation, there are also differences in clinical and epidemiological characteristics of children diagnosed during childhood based on geographical location. Indeed variation in clinical presentation can be partly due to EBV subtype and latent membrane protein (LMP)-1 variation (Rao *et al.*, 2000). Of note a novel K variant of LMP-1 has been identified among BL patients in western Kenya although the functional implication in BL pathogenesis was not determined (Wohlford *et al.*, 2013). Together these data indicate that clinical presentation can be influenced by a multiplicity of factors and there is need for studies to address these factors.

Children who presented with abdominal tumor only were more compare to those with facial tumor only or abdominal and facial tumor combined. However, a study conducted in Northern Uganda found that eBL cases presenting with either abdominal tumor only or with a combination of abdominal and facial tumor were more than those with facial tumor only (Ogwang *et al.*, 2008). This disparity might have been due to geographical variation and age differences at diagnosis, since the average age at in the current study is 7.37 years for both sexes while in Northern Uganda study it was 6 years in both girls and boys. Of significant is the finding in Nigeria study which recorded more of facial tumor presentation (Mava *et al.*, 2013).

This study also revealed an increase in children presenting with generally lymphadenopathy, malignant pleocytosis, and with symptoms such as fever, weight loss, night sweats and severe infection overtime consistent with findings from a previous study (Orem *et al.*, 2011), suggesting that the symptoms at diagnosis are similar across the region.

This study shown that HIV prevalence stood at 3.9%. Of significant is that previous studies have shown that there is an increase in HIV-related BL in East Africa (Mwanda *et al.*, 2001; Mwanda *et al.*, 2009; Orem *et al.*, 2011). Hence there is need to investigate how co-infection with HIV impacts on BL pathogenesis and tumor among children in East Africa.

This study reported a mortality rate of 34.83% which is higher than 15.96% reported in Uganda (Orem *et al.*, 2011), this can be partly attributed to the fact that the Ugandan study was carried out at the Uganda Cancer Institute where there are expert for both early diagnosis and timely initiation of the eBL patients to proper treatment. In fact a recent study in our study setting revealed that mortality in BL patients is mainly due to overdose with cyclophosphamide and doxorubicin as a result of miscalculation of dosages hence the poor treatment outcomes (Buckle *et al.*, 2016). Our data further reveal that there was an increased mortality rate in children who had no record of receiving or those who did not receive induction, consolidation and maintenance chemotherapy relative to those who received all phases of these therapies. In addition children who achieved complete remission after chemotherapy had lower mortality rate. Of a note, a study in Malawi found that increased mortality rates in BL patients were due to suboptimal supportive care (Hesseling *et al.*, 2003).

Moreover, our studies reveal that children diagnosed using histology had significantly lower mortality rate relative to those who were diagnosed through cytology indicating that there is need to validate the utility of this diagnostic techniques to ensure proper diagnosis and care for BL patients in poor resource settings (Buckle *et al.*, 2016). According to Uganda study conducted by Ogwang *et al.*, 2011, Insufficient laboratory procedures compromises the accuracy of clinical diagnosis of BL. Sensitive and specific diagnostic laboratory test is necessary to increase the quality of BL epidemiology studies and its clinical diagnosis as this will minimize the inclusion of the diseases which has same clinical presentation (Ogwang *et al.*, 2011).

A previous study revealed that the rate of mortality was more than twice the mortality rate among HIV negative children before the introduction of ARV (Orem *et al.*, 2011). Our data reveal that there was no difference in the rate of mortality by HIV status. This can be attributed to improved treatment outcomes in cancer patients with underlying HIV infection due to the integration of ARVs in treatment of the patients. In fact a recent study indicated that early diagnosis coupled with highly active antiretroviral treatment (HART) improved both the prognosis and the survival of patients with extranodal non-Hodgkin lymphomas (NHLs) (Corti, 2006). Further suggesting that incorporation of HART in treatment of cancer patients with underlying HIV infection can greatly improve both the prognosis and survival of cancer patients.

Anemia is the most common hematological abnormality associated with lymphomas (Bigegardet *et al.*, 2006; Kirchoff and Silvestri, 2008). While it is evident that the severity of anaemia is closely related to tumor progression or burden (Teuffelet *et al.*, 2008), discrepancies on both the incidences and the impact of anemia on patient survival outcomes based on tumor sub-types have been reported (Advani *et al.*, 1997; Birgegardet *et al.*, 2006). This study reveals that severe anemia ( $\leq 8$  g/dL) is associated with increased mortality rate. This is consistent with a recent study in the same hospital that revealed that children with anemia and malaria were less likely to survive relative to those without anemia and malaria. In addition those with severe anemia were less likely to survive (Buckle *et al.*, 2016). Indeed a previous study had shown that hematological abnormalities including severe anemia results in intense hematopoietic compensatory mechanisms in BL patients as evidenced by both anicytosis (variations in red cell sizes) and granulopoiesis, which may result in oxidative stress in the BL patients, consequently leading to fatal outcomes (Feruciet *et al.*, 2005).

More importantly, tumor presentation was another determinant of mortality with children presenting with testicular and lung parenchymal tumors having increased mortality rate. This can be partly attributed to these children presenting with advanced BL stage. Indeed similar findings were found in girls with ovarian mass where increased mortality was associated with advanced BL stage (Orem *et al.*, 2011).

However neither the combination of facial and abdominal nor other presentations had an association with mortality. Moreover this study found that there was neither difference in mortality based on gender, age of diagnosis nor if there was clinical diagnosis. In addition there was no association between mortality with clinical symptoms such fever, anemia, weight loss, night sweats, severe infection and malaria.

## VI. CONCLUSION AND RECOMMENDATION

### Conclusion

Endemic Burkitt's lymphoma is more prevalent among male children at the age of 5-9 years and normally it has similar clinical symptoms such as fever, anemia, weight loss, night sweating, malaria and severe infections. Its presentation has remained unchanged with facial and abdominal tumor being the most common. This Lymphoma is very responsive to chemotherapy treatment as patients who complete the entire treatment cycle up to maintenance therapy have low mortality

rate. Moreover, complete remission to treatment results in improved survival rates. eBL patients who present with lung parenchymal and testicular tumor has higher mortality rate.

Severe Anemia is one the hematological abnormalities that develops in patients diagnosed with eBL. It increases the mortality rate therefore its early diagnosis is beneficial to the patients as the children are possibly to survive with prompt management and proper nutrition. The sensitivity and specificity accuracy of the techniques used for BL diagnostic at JOOTRH calls for validation since our studies reveal that children diagnosed using histology had significantly lower mortality rate relative to those who were diagnosed through cytology.

## VII. RECOMMENDATIONS

Few children receive maintenance treatment and attend clinic after they leave the hospital. The association of not completing maintenance chemotherapy treatment and relapse of the disease need to be identified. Moreover, the healthcare providers should educate the patients and their caretakers on the

importance of attending clinic even after showing complete remission.

Patients diagnosed by cytology techniques had high mortality rate than those who had histology diagnostics. The laboratory quality assurance team therefore needs to ensure the validation of the utility of the diagnostic techniques to for proper diagnosis and care for BL patients.

Further research need to be conducted to identify the factors leading to more cases of eBL presenting with abdominal tumor in the study region compared to majority of facial presentation in the neighboring East Africa region like Uganda.

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#### AUTHORS

**First Author** – Lamék Onyango, lamekowuor@gmail.com, Department of Biological Sciences, School of Biological and Physical Sciences, Jaramogi Oginga Odinga University of Science and Technology, Kenya

**Second Author** – Dr. Amolo Asito, Phdjakogwanjo@gmail.com, Department of Biological Sciences, School of Biological and Physical Sciences, Jaramogi Oginga Odinga University of Science and Technology, Kenya.