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RESEARCH ARTICLE

Survival of children with endemic Burkitt lymphoma in a prospective clinical care project in Uganda

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Abstract

Purpose: "Endemic" Burkitt lymphoma (BL) is a common childhood cancer in Africa. Social and treatment factors may contribute to poor survival. With the aim of improving BL outcomes in Uganda, we undertook a comprehensive project (BL Project) that provided diagnostic support, access to standard chemotherapy, nutritional evaluations, and case management. We evaluated survival of children with BL in the context of the project.

Patients and methods: Patients followed by the BL Project who consented to research were enrolled in this study. Children with a pathology diagnosis consistent with BL were eligible. Data were collected prospectively. First-line chemotherapy generally consisted of six cycles of cyclophosphamide, vincristine, low-dose methotrexate (COM). We used Kaplan–Meier and Cox regression analyses to evaluate factors associated with overall survival (OS).

Results: Between July 2012 and June 2017, 341 patients with suspected BL presented to the BL Project. One hundred eighty patients with a pathology-based diagnosis were included in this study. The median age was seven years (interquartile range, 5–9), 74% lived ≥100 km from the Uganda Cancer Institute, 61% had late-stage disease, 84% had ECOG performance status < 3, 63% reported B-symptoms, and 22% showed neurologic symptoms. Fewer than 10% abandoned therapy. The four-year OS rate was 44% (95% CI, 36%–53%). In a multivariate model, ECOG status was significantly associated with mortality.

Conclusion: The BL Project reduced effects of lacking supportive care and oncology resources, and allowed patients from Uganda to receive curative intent therapy with minimal loss to follow-up. Nonetheless, OS remains unacceptably low. Improved therapeutic approaches to endemic BL are urgently needed in Africa.

KEYWORDS
Burkitt lymphoma, global health, supportive care

Abbreviation: AUS, abdominal ultrasound; BL, Burkitt lymphoma; BMA/bx, bone marrow aspirate and biopsy; CI, confidence interval; CNS, central nervous system; COM, cyclophosphamide, vincristine, methotrexate; COP, cyclophosphamide, vincristine, prednisone; CR, complete response; CSF, cerebrospinal fluid; CXR, chest x ray; eBL, endemic Burkitt lymphoma; ECOG, Eastern Cooperative Oncology Group; FFPE, formalin-fixed and paraffin-embedded; Fred Hutch, Fred Hutchinson Cancer Research Center; HR, hazard ratio; IHC, immunohistochemistry; IQR, interquartile range; KM, Kaplan–Meier; LDH, lactate dehydrogenase; LL, lymphoblastic lymphoma; LMIC, low- and middle-income countries; OS, overall survival; PD, progressive disease; PR, partial response; RD, relapsed disease; sBL, sporadic Burkitt lymphoma; SBRCT, small blue round cell tumor; SD, stable disease; SOC, standard of care; SPD, sum of the product diameter; SSA, Sub-Saharan Africa; TLS, tumor lysis syndrome; UCI, Uganda Cancer Institute; ULN, upper limit of normal.

1 | INTRODUCTION

Burkitt lymphoma (BL) is the commonest childhood cancer in many African countries, with an incidence between 5 and 10/100 000.[1–5] Burkitt and colleagues pioneered curative therapy at the Uganda Cancer Institute (UCI) in the 1950s.[6–8] In subsequent years, survival of all children with endemic BL (eBL) at the UCI has been reported between 30% and 65%, consistent with recent reports from Kenya and Malawi.[9–15] Outcomes lag behind those in high-resource settings, where >90% of children with sporadic BL (sBL) survive.[16–18]

Though differences in survival between high- and low-resource settings may be impacted by tumor biology and differences in therapy, limited healthcare resources and social factors contribute to high rates of abandonment and loss to follow-up in low-resource settings, impacting treatment options.[19–21] Patients with sBL are treated with high-intensity chemotherapy associated with significant treatment-related toxicities, including myelosuppression, mucositis, febrile neutropenia, and sepsis.[16,18,22] Optimal therapy and supportive care are compromised by stock-outs of chemotherapy, supportive drugs, and low blood product availability in low-resource settings.[19] Consequently, chemotherapy regimens implemented in high-resource countries are too toxic to be used safely in low-resource settings.[12] Chemotherapy regimens that can be safely given to children with eBL in low-resource settings are less intense with uncertain efficacy.

Improvement in eBL outcomes in Uganda depends on increased understanding of social factors affecting care, enhanced methodology for patient follow-up, and improved diagnostic and treatment capacity. To augment government support, the UCI, in collaboration with the Fred Hutchinson Cancer Research Center (Fred Hutch), initiated a clinical care project in July 2012 termed the "BL Project," with the intention of optimizing care through increased diagnostic accuracy, improved patient retention, treatment completion, and ultimately improved overall survival (OS). We report results of an analysis of OS and associated factors among children diagnosed with BL who were followed prospectively by the UCI BL Project between 2012 and 2017 and consented to the study.

2 | METHODS

2.1 | Study setting and population

Located in the capital city, Kampala, the UCI is Uganda's only tertiary oncology center serving its population of nearly 40 million people (2017). UCI receives limited government funding to support care of pediatric cancer patients. Funds cover, for example, chemotherapy, supportive care (blood products and medication); however, funds are frequently depleted, leading to significant gaps in care. Government funds do not cover pathology diagnosis, bone marrow and central nervous system (CNS) evaluation, and other important aspects of care.

The BL Project followed all patients with BL at the UCI from the time of presentation, provided chemotherapy during government stocks-outs, ensured each patient had a histologic review of their tumor biopsy, supported patient transportation to UCI, and provided case management for adherence support. Details of costs covered by the BL Project and the Ugandan government have been published elsewhere.[23] Patients with a diagnosis other than BL were not followed by the BL Project. The impact of a wrong diagnosis on the outcomes of patients was out of scope for this paper. Although the project provided meals to all children on the pediatric inpatient ward and additional nutritional support (pediatric formula) for those with cachexia, we did not evaluate the impact of this intervention on survival.

Patients followed by the BL Project were presented the opportunity to participate in this observational research study analyzing data captured as part of the BL Project. For this analysis, we included BL Project participants who were aged ≤17 years at BL diagnosis, had a clinical diagnosis of BL by a local oncologist and at least one pathology diagnosis consistent with BL, presented to UCI between July 18, 2012, and June 30, 2017, and who consented to research, or qualified for a waiver of consent, in addition to receiving clinical care (full cohort [Figure 1]). We conducted additional survival analysis on subcohorts (treated cohort and BL-COM cohort) as described below in Data collection and statistical analysis.

2.2 | Patient evaluation

Patients presenting to the UCI with suspected BL were treated in accordance with the UCI standard of care (SOC).

2.2.1 | Pathologic diagnosis

Patients clinically suspected to have BL by the treating physician underwent incisional biopsies of facial tumors in the Mulago Hospital oral surgery department or ultrasound-guided core-needle biopsy of abdominal tumors and other nonfacial tumors in the Mulago Hospital radiology department, to pathologically confirm the diagnosis. Formalin-fixed, paraffin-embedded (FFPE) tissue samples were analyzed per SOC by trained pathologists based on a review of hematoxylin and eosin-stained slides at the Makerere University pathology laboratory. As a quality assurance measure, through the BL Project, we sent tumor specimens to a private Kampala-based pathology laboratory for parallel testing. Therefore, some patients had two pathology diagnoses from separate laboratories. In cases of result discordance, the treating physician determined patient treatment.

2.2.2 | Staging

Staging was performed according to Ziegler (Supporting Information Table S2) based on chest X-ray (CXR), abdominal ultrasound (AUS), and bone marrow aspirate/biopsy (BMA/bx) when aspirate/biopsy needles were available.[24] We defined early-stage disease as Ziegler stages A and B, and late-stage disease as Ziegler stage C, D, or AR. The treating physician assessed CNS involvement through the presence of CNS symptoms, and, when available, cytological examination by wet preparations of cerebrospinal fluid (CSF) or by cytospin. Detailed

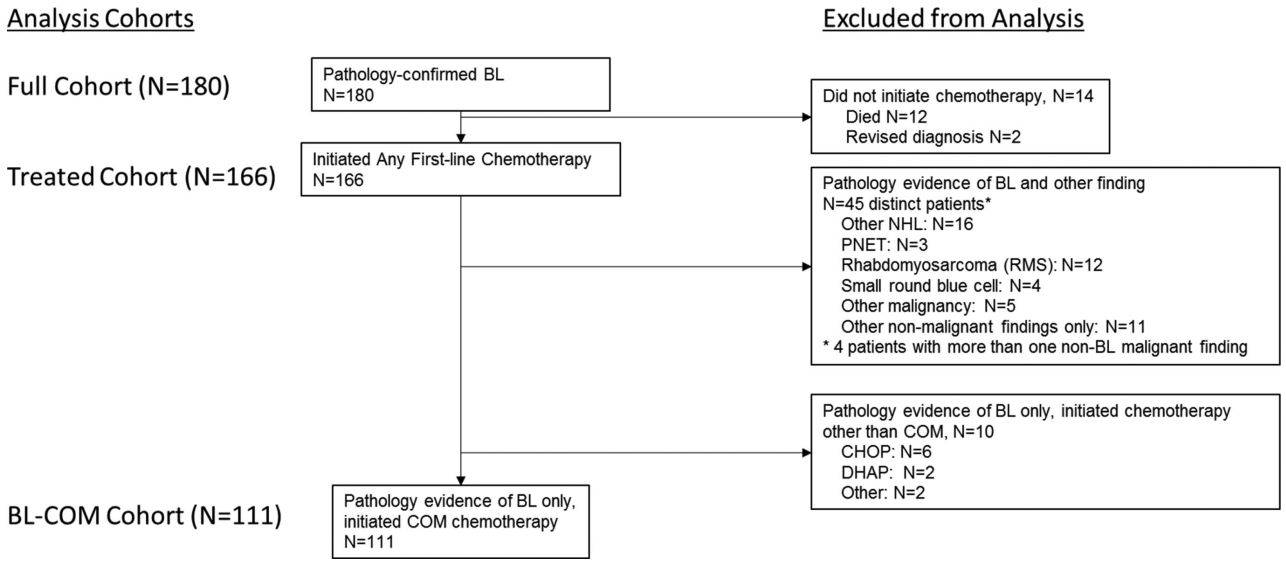

FIGURE 1 Construction of analysis cohorts. Full cohort includes all patients with clinical and histological diagnosis of BL, regardless of other histology findings ($N = 180$). Chemotherapy cohort includes the subset of patients who any initiated chemotherapy ($N = 166$). BL-COM cohort includes patients who have only histology findings indicating BL and no pathology reports with discordant findings, and who initiated COM chemotherapy ($N = 111$)

imaging to determine spinal cord compression through a non-CNS tumor was not available; therefore, any neurologic deficit is thought to be CNS involvement in the absence of the ability to clearly rule this out.

2.2.3 | Other baseline factors

Clinical evaluation of factors hypothesized to impact outcomes included Eastern Cooperative Oncology Group (ECOG) performance status, B-symptoms, duration of symptoms, complete blood count, and chemistry panel (including lactate dehydrogenase [LDH], electrolytes, creatinine, blood urea nitrogen, and uric acid). Malaria status was evaluated by blood smear microscopy. Nutritional evaluations were performed to determine if patients were healthy, moderately, or severely malnourished based on comparison of weight for height and mid-upper arm circumference to reference population values. Patients' home district, as provided by caregivers, was used to determine the distance traveled to the UCI.

2.3 | Treatment and response evaluation

First-line treatment for BL per the UCI SOC consisted of six cycles of cyclophosphamide (30 mg/kg per dose), vincristine (1.4 mg/m^2 per dose), and methotrexate (15 mg/m^2 per dose) (COM) with intrathecal administration of methotrexate (7.5 mg/ m^2) given every two weeks, or twice a week for patients with CNS involvement (Supporting Information Figure S1). This regimen has been the SOC at the UCI for decades, and limited resources did not allow for patients to receive higher intensity regimens. Beginning in 2015, selected patients were treated with a debulking regimen comprising cyclophosphamide (500 mg/m^2) vincristine (1 mg/m^2) and prednisone (60 mg/m^2) (COP) until patients were stable to receive COM (Supporting Information Figure S1). BL patients typically received the first two COM cycles as inpatient, and later cycles as outpatients. After six cycles of COM, patients were assessed for response to treatment via CXR, AUS, CSF analysis, and BMA/Bx.

Tumor size was measured using the sum of the product of diameters (SPD) (longest overall tumor diameter and longest diameter perpendicular to the longest overall diameter on imaging or as measured on physical exam for facial tumors). Responses were defined as: complete response (CR) 100%, partial response (PR) $\geq$ 50% $<$ 100%, stable disease (SD) $<$ 50% decrease in tumor size, progressive disease (PD) increase in tumor size, and relapsed disease (RD) as disease recurrence. At the discretion of the treating physician, patients who did not respond, relapsed, or were perceived to have particularly aggressive disease were treated with second-line therapy.

2.4 | Follow-up and vital status assessment

After completing treatment, patients attended clinical follow-up visits monthly for three months, then every three months for nine months according to UCI SOC. BL Project case managers contacted patients by telephone if they missed a scheduled follow-up. Subsequently, to ascertain the vital status of surviving patients, case managers conducted active follow-up of all patients approximately every six months starting in August 2016. Active follow-up was discontinued if two contacts were unsuccessful within six months. Attribution of cause of death was determined in the BL cohort, based on documentation of infection, neutropenia, relapse, and/or PD, and the timing of death relative to therapy.

2.5 | Data collection and statistical analysis

Under the BL Project, data on participants were prospectively collected on case report forms and entered into an electronic database

with appropriate quality controls. Baseline characteristics were summarized as frequencies and percentages, or medians and interquartile ranges (IQR). We used Kaplan–Meier (KM) methods to estimate OS from the date of enrollment in the project until the earliest of death, change in diagnosis, or last date the patient was confirmed alive, or December 31, 2017. We conducted two additional survival analyses in the same manner but starting from the date of initiation of chemotherapy: (i) all study patients who initiated any chemotherapy regimen (chemotherapy cohort); (ii) patients with histology diagnosis of BL and no conflicting secondary histology diagnosis who initiated COP or COM (BL-COM cohort; Figure 1). For KM analysis stratified by stage, we omitted patients without stage information.

We used univariate Cox regression to estimate hazard ratios (HR) with robust 95% confidence intervals (CI). For this analysis, we included patients' missing information for independent variable(s) in a separate category. We conducted separate regression analyses with time zero defined as the date of enrollment into BL Project for the full cohort analysis, and date of initiation of treatment for the chemotherapy and BL-COM subgroup analyses. Multivariate Cox regression included age and variables significantly ($P < 0.05$) associated with risk of mortality in univariate analysis that had few missing values for patients. We used Stata versions 14 and 15 (StataCorp, College Station, Texas).

2.6 | Ethics

This study received ethical approval from Fred Hutch Institutional Review Office, UCI Research Ethics Committee, and the Uganda National Council for Science and Technology. Parents of patients actively followed at the UCI signed consent in English or Luganda and children older than eight years provided assent. We received a waiver of consent for patients who died or were lost to follow-up for ≥6 months.

3 | RESULTS

3.1 | Diagnosis and study enrollment

Of 341 children with suspected BL who presented to UCI between July 18, 2012, and June 30, 2017, 180 met our eligibility criteria for the full cohort (Figure 1) and were included in this analysis. Sixty-six of 161 excluded patients had an alternative cancer diagnoses, most commonly other lymphomas ($N = 24$) or rhabdomyosarcoma ($N = 14$).

3.2 | Baseline characteristics

The median age of the 180 patients with confirmed BL was seven (IQR: 5–9), and 62% were male (Table 1). Seventy-four percent of patients lived ≥100 km from UCI. The majority of patients ($N = 109$, 61%) were diagnosed with late-stage disease (Ziegler C, D, or AR). Workup identified 75 (42%) patients with abdominal tumors, 52 of which also had one or more nonabdominal tumors, while 79 (44%) subjects had only face, head, or neck tumors. Imaging data were not available for 20 (11%) patients (seven of these died within seven days of presentation). Based on a nutritional assessment conducted on 113 (63%) patients, 27 (24%) patients were malnourished.

Of 134 patients with measured LDH, 78 were above twice the upper limit of normal (Table 1). Most patients (84%) had ECOG performance index < 3. Sixty-three percent reported B-symptoms and 22% had symptoms consistent with CNS involvement (e.g., paralysis). Eighty-four percent ($N = 151$) had a baseline lumbar puncture to assess for CNS involvement. The majority ($N = 81$) of CSF analyses were performed by wetprep, which was positive in one patient. For 59 patients who had cytospin performed on the CSF, five (8%) were positive for disease involvement. Anemia (hemoglobin < 11 g/dL) was present in 114 patients (63%).

3.3 | Treatment

Of 180 patients with confirmed BL, 166 patients (92%) started chemotherapy, 12 (7%) died prior to initiating treatment, and two received a revised diagnosis other than BL prior to starting therapy (Figure 1). COM was the most common regimen initiated ($N = 146$, 88%; Table 2). For 73% of treated patients, first-line therapy was initiated within seven days of confirmatory pathology results. Following the start of first-line chemotherapy, 91% of all cycles were administered within seven days of schedule, 7% were 7 to 13 days late, and 2% were ≥14 days late.

Of 166 patients initiating chemotherapy, 105 (63%) children completed ≥6 cycles of first-line chemotherapy (Table 2). Those patients who did not complete six cycles of first-line therapy either initiated second-line therapy ($N = 11$), died ($N = 25$), were lost to follow-up ($N = 9$, 5%), received a revised diagnosis ($N = 13$), or were last known to be alive within six months of December 31, 2017 ($N = 3$).

Of 180 patients, two patients' families refused treatment; these patients subsequently died. Of 166 patients initiating chemotherapy, 14 (8%) discontinued first-line chemotherapy before completion against physician guidance; seven of which are known to have died. Overall treatment abandonment (defined as refusing tumor-directed therapy or discontinuing therapy prior to completion of the prescribed regimen for reasons other than death) was < 10%.

3.4 | Survival analysis

Only 5% of patients were lost to follow-up. The median follow-up was 9.1 months (IQR, 3.0–32.4 months) among all patients, and 20.7 months (IQR, 6.5–46.4 months) among surviving patients (Supporting Information Figure S2). OS at four years was 44% (95% CI, 36%–53%; Figure 2A). Survival was significantly longer for early-stage patients (50%; 95% CI, 36%–63%) compared with late-stage patients (42%; 95% CI, 31%–53%; log-rank $P = 0.04$). For 166 children who initiated chemotherapy (chemotherapy cohort), OS following the start of chemotherapy was 48% (95% CI, 38%–56%; Figure 2B). For this subgroup, the difference in OS between patients with early-stage disease

TABLE 1 Characteristics of pediatric Burkitt Lymphoma patients at enrollment, Uganda Cancer Institute, July 2012–June 2017

	Full cohort *N* = 180		Chemotherapy cohort *N* = 166		BL-COM cohort[a] *N* = 111	
Median age, years (IQR)	7	(5–10)	7	(5–10)	7	(5–9)
	N	%	*N*	%	*N*	%
Age ≥10 years	47	26	42	25	26	23
Male	112	62	101	61	68	61
Distance to clinic (km)						
<100	47	26	43	26	27	24
100–149	48	27	45	27	33	30
150–199	31	17	28	17	17	15
≥200	54	30	50	30	34	31
Malaria						
Negative	97	54	92	55	63	57
Positive	11	6	10	6	7	6
Unknown	72	40	64	39	41	37
Nutrition status						
Normal	86	48	84	51	66	59
Malnourished	27	15	26	16	16	14
Unknown	67	37	56	34	29	26
Hemoglobin (g/dL)						
< 8	18	10	16	10	8	7
8–9.9	53	29	48	29	34	31
10–10.9	43	24	41	25	30	27
≥11	58	32	56	34	35	32
Unknown	8	4	5	3	4	4
ECOG performance status						
0–1	87	48	87	52	61	55
2	64	36	58	35	36	32
3–4	29	16	21	13	14	13
Duration of symptoms						
≤1 Month ago	59	33	55	33	39	35
1–3 Months ago	58	32	52	31	36	32
4–6 Months ago	15	8	14	8	10	9
> 6 Months ago	10	6	8	5	4	4
Unknown	38	21	37	22	22	20
Any B-symptoms reported						
No	25	14	25	15	16	14
Yes	113	63	99	60	68	61
Unknown	42	23	42	25	27	24
Any CNS symptoms reported						
No	141	78	133	80	87	78
Yes	39	22	33	20	24	22
CSF cytospin assay result						
Negative	54	30	52	31	34	31
Positive	5	3	5	3	5	5
Unknown	121	67	109	66	72	65

(Continues)

TABLE 1 (Continued)

	Full cohort N = 180			Chemotherapy cohort N = 166			BL-COM cohort[a] N = 111		
Stage									
A or B	68	38		66	40		44	40	
C, D, or AR	109	61		99	60		66	59	
Unknown	3	2		1	1		1	1	
Tumor site(s)									
Face, head, or neck only	79	44		76	46		45	41	
Abdominal involvement	75	42		70	42		54	49	
Any other combination	6	3		6	4		4	4	
Unknown	20	11		14	8		8	7	
Lactose dehydrogenase ≥2 × ULN									
No	56	31		55	33		41	37	
Yes	78	43		69	42		43	39	
Unknown	46	26		42	25		27	24	
Bone marrow involvement									
Negative	75	42		74	45		51	46	
Positive	8	4		7	4		4	4	
Unknown	97	54		85	51		56	50	
Laboratory measurements	*N*	Median	IQR	*N*	Median	IQR	*N*	Median	IQR
Hemoglobin g/dL	172	10	9–12	161	10	9–12	107	10	9–11
Neutrophil count cells 10^3/μL	172	4	2.6–5.4	161	4	2.5–5.4	107	4	2.6–5.2
White blood cell Count cells 10^3/μL	172	8	6.3–10.2	161	8	6.3–9.9	107	8	6.1–9.8
Platelets 10^3/μL	172	333	252–456	161	332	253–449	107	333	253–434
Lactose Dehydrogenase U/L	134	551	341–1069	124	496	341–893	84	474	336–859

Abbreviations: CNS, central nervous system; CSF, cerebrospinal fluid; COM, cyclophosphamide, vincristine, and methotrexate; COP, cyclophosphamide, vincristine, and prednisone; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; ULN, upper limit of normal range.
[a]BL-COM cohort: Patients with only BL histology findings and initiating treatment with COM (or COP only).

(OS = 51%; 95% CI, 37%–63%) and patients with late-stage disease (OS = 46%; 95% CI, 34%–57%) was not statistically significant (log-rank $P = 0.16$).

Of 111 patients who had histology results indicating BL, with no conflicting potential diagnosis, and were treated with COM (BL-COM cohort, Figure 1), 76 completed ≥6 cycles. Of these, 55 (72%) had a CR, 9 (12%) a PR, 3 (4%) PD or RD after the sixth cycle of COM, but 9 (12%) had no response assessment. In the entire BL-COM cohort ($n = 111$), 24 patients had incomplete response (PR and PD) and 16 had RD. Among 47 deaths in the BL Cohort (12 tumor, 10 infection, 3 infection and tumor, 1 organ failure, 21 unknown causes), 27 (57%) occurred in the setting of RD or PD. Eleven of 47 patients died within 30 days of receiving first-line COP-COM therapy (5 infection, 3 tumor and infection, 1 organ failure, 2 unknown causes). In the BL-COM cohort, 29 patients experienced severe neutropenia (absolute neutrophil count < 500). Only three patients who developed severe neutropenia died within 30 days of the neutropenic episode.

The median follow-up for all 111 patients in the BL-COM cohort was 13.8 months (IQR, 5.7–40.1 months), and 37.2 months (IQR, 7.9–47.4 months) among surviving patients (Supporting Information Figure S2). OS at one year was 64% (95% CI, 53%–72%) but fell to 50% (95% CI, 39%–60%) by four years (Figure 2C). OS was higher for patients with early-stage disease (OS = 57%; 95% CI, 40%–71%) compared with late-stage disease (OS = 45%; 95% CI, 31%–58%), although the difference was not statistically significant (log-rank $P = 0.09$).

In univariate analyses, patient characteristics significantly associated with higher risk of mortality in the full cohort included higher ECOG status (ECOG 3/4 compared with 0/1, HR 3.82; 95% CI, 1.97–7.42; $P < 0.001$) and late-stage disease (HR 1.60; 95% CI, 1.03–2.48, $P = 0.04$; Supporting Information Table S1). The strength of univariate associations of clinical and personal characteristics with mortality among the chemotherapy cohort ($n = 166$) and the BL-COM cohort ($N = 111$) was similar (Supporting Information Table S1). Some additional baseline variables were significantly associated with mortality, though a significant proportion of patients had missing information; therefore, these must be interpreted with care. These include malnutrition (HR 2.38; 95% CI, 1.31–4.33; $P < 0.001$), elevated LDH (HR 1.81; 95% CI, 1.11–2.95, $P = 0.02$), and bone marrow involvement (HR 4.03; 95% CI, 1.55–10.5; $P < 0.001$).

In multivariate analysis, only ECOG performance status remained significantly associated with mortality (Table 3) in the full cohort (3/4 compared with 0/1, HR 3.20; 95% CI, 1.57–6.50; $P = < 0.001$), the

TABLE 2 Summary of treatments received by pediatric Burkitt lymphoma patients at the Uganda Cancer Institute, 2012–2017

	N (*N* = 166)	%
First-line chemotherapy		
COM[a]	146	88
CHOP	9	5
DHAP	2	1
Other	2	1
COP only	7	4
Received COP prior to first-line	40	24
First-line cycles		
COP only	7	4
1–5	54	33
6	80	48
7–9	25	15
Second-line regimens[b]		
COM	0	0
CHOP	12	26
DHAP	31	67
Other	2	4
Unknown	1	2
First-line response[c]		
Complete response	70	67
Partial response	13	12
Progressive disease/relapse	9	9
Unknown	13	12

Abbreviations: COM, cyclophosphamide, vincristine, and methotrexate; COP, cyclophosphamide, vincristine, and prednisone; CHOP, cyclophosphamide, vincristine, doxorubicin, and prednisone; DHAP, dexamethasone, cytarabine, platinol.

[a]Includes one patient who received one cycle of R-COM and no further treatment; one patient who received one cycle of VDC followed by a complete COM regimen; and one patient who received one cycle of (lymphoblastic lymphoma-type therapy) followed by a complete COM regimen.

[b]Among 37 patients receiving any second-line therapy.

[c]Among 105 patients receiving 6 or more cycles (excluding COP).

chemotherapy cohort (3/4 compared with 0/1, HR 2.44; 95% CI, 1.11–5.39; $P = 0.03$), and the BL-COM cohort (2 compared with 0/1, HR 2.53; 95% CI, 1.2–5.32, $P = 0.01$).

4 | DISCUSSION

Quality improvement projects, such as the BL Project, are crucial to elevating outcomes of cancer treatment in low-income countries. This project minimized treatment delays, provided transportation subsidies to 98% of BL patients, and filled one or more pharmacy stockouts of chemotherapy or supportive medicine for over 100 patients. All patients received a daily meal while on the UCI pediatric ward. For patients with signs of malnutrition, the project provided nutritional support. With these interventions, the BL Project's loss to follow-up and treatment abandonment were low compared with historical attrition at UCI (unpublished data 30%). Although not designed to evaluate the relative survival benefits of the project components, the project demonstrated the feasibility of administering curative intent therapy in a timely manner with relatively low loss to follow-up in a low-resource setting. This allowed for a more accurate estimate of the efficacy of COM, including OS, by minimizing social factors.

Despite the success of the BL Project in addressing treatment gaps, survival of children with BL remained far below that of children in more affluent countries. A recent report from Malawi showed promising 72% 12-month OS results in 42 children with stage III/IV disease with the use of two doses of doxorubicin.[25] Other analyses conducted within the Sub-Saharan African (SSA) region reported OS as 45% in Kenya and 33% to 63% in Malawi depending on tumor site location.[9,26] Collectively, these findings and our report highlight the need for improvements to the COM regimen as well as appropriate supportive care to improve survival of children with BL in SSA.

In univariate analyses, several baseline factors were associated with survival, including malnutrition, high ECOG status, late-stage, abdominal tumors, and high LDH. All of these factors represent clinical manifestations of tumor burden and are consistent with previous findings in high-income settings.[18,22] Importantly, demographic factors analyzed were not associated with OS, emphasizing the importance of tumor biology. In our multivariate model including age, ECOG status, stage, and tumor site, ECOG status was the only significant prognostic factor.

This analysis has several limitations. First, incomplete data on LDH limited our ability to assess the prognostic value of LDH in this analysis. Improved low-cost risk stratification schemes are needed in SSA.[27] The association of LDH and high-risk disease demonstrated for NHL treated in high-income countries is documented in reports from Malawi and Kenya and likely remains an important, low-cost blood-based prognostic biomarker useful in eBL.[9,26] Another important limitation in this analysis was inadequate methods for staging the CNS and incomplete staging in general. This is in part due to lack of standard-of-care risk-stratified treatment approaches to eBL. It should be a priority to allocate additional resources to ensure complete staging (CNS, bone marrow, and adequate imaging). These factors could have impacted staging accuracy and may explain why we did not observe a greater survival benefit for early-stage disease. Lastly, our analysis enrolled patients followed by the BL Project through informed consent or waiver. Some patients successfully treated by the BL Project did not consent to participate in the research analysis. Therefore, we may be underestimating the true OS. However, we believe that this has a small impact on our estimation since we were able to capture most patients who presented to the UCI during the analysis period.

The reason for the disappointingly low OS may be a combination of several factors. Advanced presentation remains an important cause of mortality. Eight percent of patients in the BL Project never received chemotherapy, many because of presentation with advanced disease. Improvements in survival may be possible with promotion of early presentation through outreach and education programs teaching providers in rural areas about the signs and symptoms of cancer. Several such efforts are being piloted in Africa aiming to reduce delayed presentation.[28,29] Our data did not show a high rate of treatment-related mortality, with most known causes of death related to tumor.

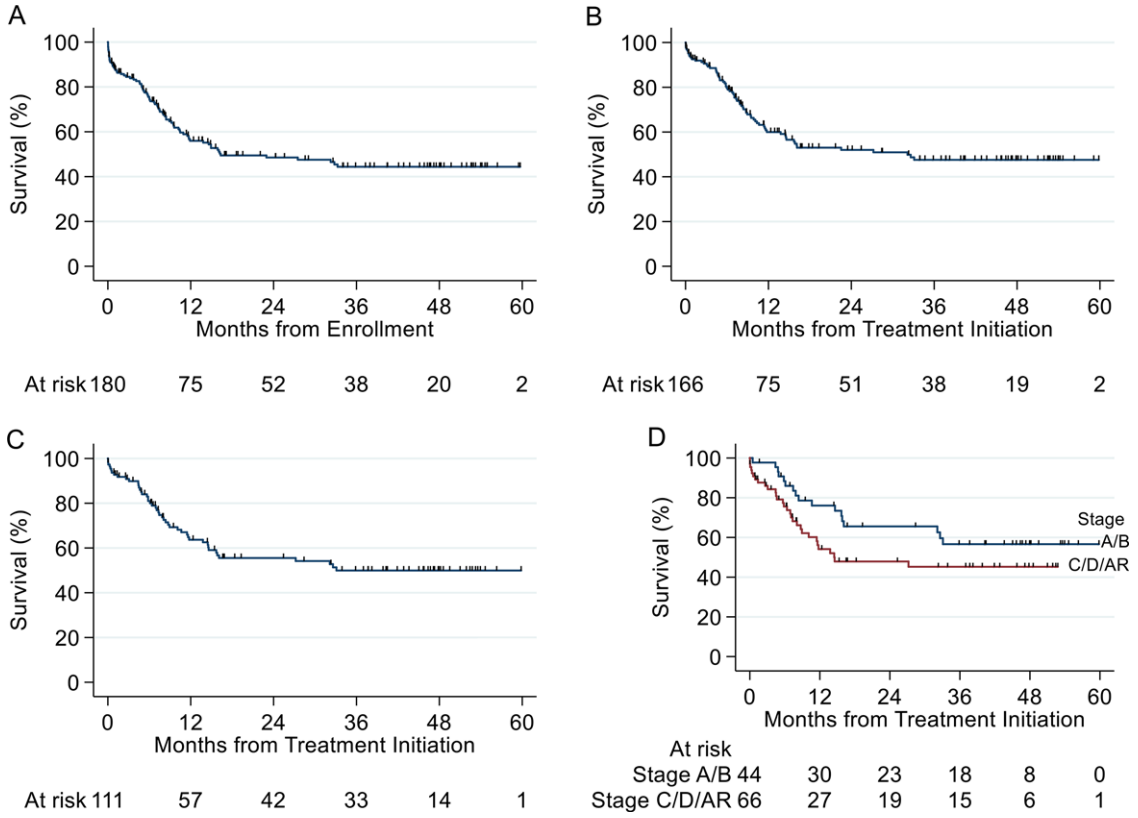

FIGURE 2 KM survival curves. (A) Entire cohort ($N = 180$) from enrollment, median survival, 16.3 months (B) all patients beginning any chemotherapy ($N = 166$) from treatment initiation, median survival, 32.1 months; (C) patients with exclusively BL histology findings and initiating COM chemotherapy ($N = 111$), median survival, 33.1 months; (D) patients with exclusively BL histology findings and initiating COM chemotherapy ($N = 111$), stratified by stage (one patient without staging information omitted), median survival not observed for early-stage (A/ B) and 14.5 months for late-stage (C/D/ AR) patients

TABLE 3 Results of multivariable Cox regression analysis of the association of patient characteristics with mortality among pediatric Burkitt lymphoma patients, Uganda Cancer Institute, 2012–2017

	Full cohort $N = 180/82$ deaths			Chemotherapy cohort $N = 166/70$ deaths			BL-COM[a] $N = 111/47$ deaths		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Age (y)									
< 10	Ref			Ref			Ref		
≥10	0.67	(0.36–1.26)	0.22	0.65	(0.34–1.25)	0.20	0.68	(0.31–1.50)	0.34
ECOG performance status									
0–1	Ref			Ref			Ref		
2	2.64	(1.53–4.54)	<0.001	2.59	(1.46–4.59)	0.00	2.53	(1.20–5.32)	0.01
3–4	3.20	(1.57–6.50)	<0.001	2.44	(1.11–5.39)	0.03	1.48	(0.50–4.37)	0.47
Stage									
Early stage (A or B)	Ref			Ref			Ref		
Late stage (C, D, or AR)	1.31	(0.66–2.61)	0.43	1.10	(0.52–2.33)	0.81	1.15	(0.22–6.15)	0.87
Unknown	2.46	(0.25–24.24)	0.44						
Tumor site(s)									
Face only	Ref			Ref			Ref		
Any abdomen	0.79	(0.38–1.63)	0.52	0.95	(0.43–2.11)	0.89	1.12	(0.18–6.92)	0.90
Other combination	0.45	(0.06–3.42)	0.44	0.51	(0.06–4.19)	0.53	0.73	(0.08–6.73)	0.78
Unknown	2.03	(0.73–5.62)	0.17	1.83	(0.54–6.25)	0.33	1.91	(0.18–19.88)	0.59

Abbreviations: COM, cyclophosphamide, vincristine, and methotrexate; COP, cyclophosphamide, vincristine, and prednisone
[a]BL-COM cohort: Patients with only BL histology findings and initiating treatment with COM (or COP only).

Therefore, our data add to a growing literature, as recently reviewed by Gopal and Gross, suggesting that interventions to increase cure rates above those achievable with COM and other low-intensity BL treatment regimens will require improved treatments that address the rapid proliferation rate of c-myc–driven lymphomas.[27] Efforts are ongoing at UCI to improve supportive care to enable administration of higher intensity regimens, inclusive of higher doses of methotrexate to achieve deeper remissions and better CNS prophylaxis, which has shown promising results in SSA.[30] Other risk-adapted regimens based on weekly cyclophosphamide for lower-risk disease with intrathecal CNS prophylaxis, and the addition of vincristine and higher dose methotrexate for higher stage disease, have also shown promising results in LMIC.[31]

High survival rates in more affluent countries are achieved with an intensive regimen of well-established chemotherapy agents and CNS-directed therapy.[16] Side effects from this therapy can be managed by health care providers using adequate supportive care measures.[17,22] In the absence of these, intensive treatment is associated with high rates of morbidity and mortality, as demonstrated by previous introduction of modified, higher intensity regimen for BL patients in Africa.[13,14] Such experiences demonstrate the complexities of treating children with BL and other cancers in LMIC. Efforts to improve curative regimens will require the concurrent development of programs, such as the BL Project, addressing supportive care and resource- and risk-adapted chemotherapy regimens.[32,33]

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CONFLICTS OF INTEREST

C.C.: *Up to Date*: Patents and royalties; *TempTime*: Consultancy, travel, accommodation, expenses; *Janssen*: Consultancy, research funding; *GSK*: Travel, accommodation, expenses; *Roche:* Consultancy, travel, accommodation, expenses.

S.MG.: *Employment: Seattle Genetics starting October 1, 2017*

T.U.: *Celgene and NCI*: Patent and royalties, research support; *Merck*, Research support

DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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