original reports abstract

Treatment of Hodgkin Lymphoma With ABVD Chemotherapy in Rural Rwanda: A Model for Cancer Care Delivery Implementation

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PURPOSE Hodgkin lymphoma (HL) is highly curable in high-income countries (HICs), yet many patients around the world do not have access to therapy. In 2012, cancer care was established at a rural district hospital in Rwanda through international collaboration, and a treatment protocol using doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) without radiotherapy was implemented.

METHODS We conducted a retrospective cohort study of all patients with confirmed HL seen at Butaro Hospital from 2012 to 2018 to evaluate quality indicators and clinical outcomes.

RESULTS Eighty-five patients were included (median age, 16.8 years; interquartile range, 11.0-30.5 years). Ten (12%) were HIV positive. Most had B symptoms (70%) and advanced stage (56%) on examination and limited imaging. Of 21 specimens evaluated for Epstein-Barr virus, 14 (67%) were positive. Median time from biopsy to treatment was 6.0 weeks. Of 73 patients who started ABVD, 54 (74%) completed 6 cycles; the leading reasons for discontinuation were treatment abandonment and death. Median dose intensity of ABVD was 92%. Of 77 evaluable patients, 33 (43%) are in clinical remission, 27 (36%) are deceased, and 17 (22%) were lost to follow-up; 3-year survival estimate is 63% (95% CI, 50% to 74%). Poorer performance status, advanced stage, B symptoms, anemia, dose intensity $< 85\%$, and treatment discontinuation were associated with worse survival.

CONCLUSION Treating HL with standard chemotherapy in a low-resource setting is feasible. Most patients who completed treatment experienced a clinically significant remission with this approach. Late presentation, treatment abandonment, and loss to follow-up contribute to the discrepancy in survival compared with HICs. A strikingly younger age distribution in our cohort compared with HICs suggests biologic differences and warrants further investigation.

JCO Global Oncol 6:1093-1102. © 2020 by American Society of Clinical Oncology

INTRODUCTION

Hodgkin lymphoma (HL) is a B-cell lymphoid malignancy that affects children and adults worldwide, yet there is a vast outcome gap between high- and low-resource settings.[1] GLOBOCAN 2018 estimated 6,893 new cases of HL (age-standardized rate, 0.77 per 100,000) and 3,111 deaths in sub-Saharan Africa (0.42 per 100,000), with a projected 78% increase in new cases by 2040.[2] By comparison, in the United States, there were more new cases (9,265) but significantly fewer deaths (1,057) in 2018, with respective age-standardized rates of 2.5 and 0.19 per 100,000.[2]

Since its introduction in 1975, the combination of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) has emerged as the most commonly used treatment of HL.[3] Current international guidelines recommend ABVD alone or in combination with radiotherapy for early-stage disease and ABVD alone for advanced-stage disease. In limited-stage nonbulky HL, ABVD alone confers an 87% 12-year freedom from progression in high-income countries (HICs).[4] In advanced disease, ABVD is associated with 5-year failure-free survival rates of 61%-63%.[5,6] Given excellent outcomes in HL, the focus of research in HICs has turned to de-escalation strategies to minimize sequelae of treatment.

Although ABVD has been the standard of care for HL for 40 years and all 4 drugs are off patent, relatively affordable, and included in the WHO Model List of Essential Medicines,[7] many patients in low- and middle-income countries (LMICs) do not have access to this curative therapy. Successful treatment of HL requires a cancer care delivery system that includes at a minimum diagnostic pathology; reliable access to chemotherapy and related consumables; and providers trained in chemotherapy mixing, administration,

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Accepted on April 28, 2020 and published at ascopubs.org/journal/go on July 17, 2020: DOI https://doi.org/10.1200/GO.20.00088

CONTEXT

Key Objective

How can we approach treatment of curable cancers like Hodgkin lymphoma in low-resource settings? Here, we evaluated a cancer care delivery system established in rural Rwanda using Hodgkin lymphoma as a model.

Knowledge Generated

In this retrospective cohort study of 77 adults and children with Hodgkin lymphoma, implementation of standard chemotherapy treatment within a basic cancer care delivery system resulted in a 63% 3-year overall survival. Evaluation of both quality indicators and clinical outcomes through an implementation science approach identified targets for system-level improvements.

Relevance

Achieving equity for patients with cancer in low-resource settings will involve coordinated efforts and innovative approaches to implement treatments that are known to be effective into diverse settings. This study demonstrates how rigorous evaluation of quality indicators and clinical outcomes in a cohort study informs cancer care delivery implementation and improvement in low-resource settings, such as rural Rwanda.

and supportive care.[8] Because ABVD is a low-intensity outpatient regimen with curative potential as a single-modality treatment, it serves as an informative model for the evaluation of cancer care delivery implementation.

In 2012, the first cancer center in Rwanda was established at Butaro District Hospital by the Rwandan Ministry of Health (MOH) with support from the nongovernmental organization Partners In Health (PIH), the Dana-Farber Cancer Institute, and other partners.[9] Within this care delivery system, a treatment protocol using 6 cycles of ABVD was implemented for pediatric and adult patients. Here, we report our patient characteristics, quality indicators, and clinical outcomes after the first 7 years. Few reports have described HL treatment implementation strategies and outcomes in low-income countries and fewer still from rural sub-Saharan Africa. Our approach addresses calls for a cancer groundshot initiative focused on the implementation of treatments already known to work and strategies that can be applied globally to reduce cancer morbidity and mortality.[10-12]

METHODS

Implementation Strategy

The Butaro Cancer Center of Excellence (BCCOE) is located in rural northern Rwanda, approximately 90 km (a 2.5-hour drive) from the capital city of Kigali. Through international collaboration, BCCOE provides basic services across the cancer care continuum: pathologic diagnosis, x-ray and ultrasound (and referrals for computed tomography [CT]), surgery, chemotherapy, referrals for radiotherapy, palliative care, and socioeconomic support.[9] Initially, biopsy specimens were sent to US partner site Brigham and Women's Hospital (BWH) for diagnosis, and subsequently, diagnostic pathology with immunohistochemistry (IHC) and telepathology consultation were established at BCCOE.[13] With no oncologists permanently onsite, care is delivered by internists, pediatricians, general practitioners, and nurses through a task shifting model.[13a] Management is guided by clinical protocols adapted to available resources, and clinicians consult with international advisors over weekly teleconferences and e-mail. Systems have been established to promote protocol adherence, such as electronic chemotherapy orders, comprehensive clinical forms, and patient tracking measures to address loss to follow-up. As the first national referral center for cancer care in Rwanda, BCCOE has enrolled $>$ 11,000 patients since 2012, and the program continues to evolve as oncology capacity expands in the country.

HL Protocol

The BCCOE protocol for HL was developed and endorsed by the MOH in 2012. The protocol requires a core needle or excisional biopsy and histology review with IHC for diagnosis. Clinical staging by physical examination according to Ann Arbor guidelines is required; chest x-ray and abdominal ultrasound (or CT if feasible) and bone marrow evaluation are recommended but do not change management. All candidates for therapy, regardless of stage, are treated with 6 cycles of ABVD (doxorubicin 25 mg/m^2 intravenously [IV], bleomycin 10 U/m^2 IV, vinblastine 6 mg/m^2 IV, and dacarbazine 375 mg/m^2 IV) given on days 1 and 15 of every 28-day cycle. Treatment response is primarily assessed by physical examination; radiographic response is not routinely assessed given the absence of second-line treatment options. Radiotherapy was not available in Rwanda during the study period. After treatment, patients are followed for surveillance. Biopsy confirmation is recommended in cases of suspected relapse.

Study Patients

All patients who presented to BCCOE from July 2012 to June 2018 and had biopsy-confirmed HL were included. Patients who received prior chemotherapy elsewhere were excluded from analysis of treatment quality indicators and clinical outcomes.

TABLE 1. Patient Characteristics

Characteristic	No. (%)
Demographic and pathologic (N = 85)	
Age, years	
Median (IQR)	16.8 (11.0-30.5)
Mean (range)	22.3 (4.1-66.9)
Sex	
Male	49 (58)
Female	36 (42)
Country	
Rwanda	74 (87)
Burundi	5 (6)
Democratic Republic of Congo	4 (5)
Other	2 (2)
HIV status	
Positive	10 (12)
Negative by laboratory result (n = 61) or self-report (n = 14)	75 (88)
Histologic subtype (n = 74)	
Classic HL, nodular sclerosis	39 (53)
Classic HL, mixed cellularity	27 (36)
Classic HL, lymphocyte depleted	5 (7)
Classic HL, lymphocyte rich	2 (3)
Nodular lymphocyte predominant	1 (1)
EBV status (available in n = 21)	
Positive	14 (67)
Negative	7 (33)
Clinical (n = 77)	
ECOG performance status (n = 62)	
0	41 (66)
1	11 (18)
2	5 (8)
3	4 (6)
4	1 (2)
Ann Arbor stage[a]	
I	11 (14)
II	23 (30)
III	25 (33)
IV	18 (23)
Cotswold modifications	
B symptoms (n = 76)	53 (70)
Bulky disease (n = 65)	16 (25)
Extranodal contiguous extension (n = 72)	10 (14)
IPS risk factors[b] (n = 77)	
Age ≥ 45 years	8 (10)
Hemoglobin < 10.5 g/dL	39 (51)
WBC count ≥ 15,000/μL (n = 76)	9 (12)
Lymphocyte count < 600/μL or < 8% of WBC count (n = 75)	13 (17)

Abbreviations: EBV, Epstein-Barr virus; ECOG, Eastern Cooperative Oncology Group; HL, Hodgkin lymphoma; IPS, International Prognostic Score; IQR, interquartile range.

[a]On the basis of physical examination and available staging evaluations.

[b]Serum albumin levels were not measured because of availability limitations.

Data Collection and Statistical Analysis

Data abstraction from clinical charts was performed using the Ona database platform (Ona Systems, Nairobi, Kenya). Variables included demographics, pathologic characteristics, HIV status, Eastern Cooperative Oncology Group (ECOG) performance status, Ann Arbor stage, International Prognostic Score (IPS) risk factors, treatment intervals, dose intensity, and survival status as of December 2019. Frequencies, medians, and ranges were used to describe the patient and disease characteristics and quality indicators, and distributions were compared using Pearson χ^2 or Wilcoxon rank sum test. Kaplan-Meier methods with log-rank tests were used to compare times from diagnosis to mortality across subpopulations. All analyses were performed using Stata 15 (StataCorp, College Station, TX).

Dose intensity of ABVD was calculated using published methods.[14] In cases where treatment was discontinued early, dose intensity was calculated for completed cycles only. Treatment was considered delayed if administered $>$ 1 week past due. Clinical complete response was determined on the basis of documented reduction in lymphadenopathy to $\leq$ 1 cm by physical examination. Relapse was determined on the basis of documented clinical suspicion, with radiographic or pathologic confirmation available in some cases. Vital status was determined by clinical records and contact with patients or families. Patients were considered lost to follow-up if they missed their most recent appointment, had no contact with BCCOE for $>$ 6 months, and were not reachable. This study was approved by the Rwanda National Ethics Committee (Kigali, Rwanda) and the Inshuti Mu Buzima Research Committee (Kigali, Rwanda).

RESULTS

Eighty-five patients with biopsy-confirmed HL were seen at BCCOE. Patient characteristics are listed in Table 1, with age distribution shown in Fig 1. Half were children $\leq$ 16 years old, and a quarter were $<$ 11 years old. Nodular sclerosis was the most prevalent histologic subtype (53%). The 10 patients who were HIV positive (12%) were older than those who were HIV negative (median age, 35.9 *v* 16.0 years, respectively; $P < .01$) and trended toward predominantly female (70% *v* 39%; $P = .06$), with similar stage and histology distributions. Epstein-Barr virus (EBV) was positive in 14 (67%) of 21 specimens assessed by EBV-encoded RNA in situ hybridization. There were no significant differences in age, sex, histologic subtype, stage, or HIV status by EBV status, although numbers were small. A majority presented with stage III or IV (56%) and B symptoms (70%) but with good ECOG performance status (0-1 in 84%). IPS risk factors, which are associated with poorer prognosis in other settings,[15] were only present in a minority of patients, with the exception of anemia in 51%.

Quality indicators related to care delivery are listed in Table 2. In most patients, the final pathologic diagnosis was made at either BCCOE (42%) or BWH (25%) and confirmed with IHC (61%). Staging chest x-rays were usually obtained (86%), but a minority had an abdominal ultrasound (35%), bone marrow evaluation (22%), or any CT scan (18%). Patients staged with CT had a similar stage distribution to those who were not. The median time from initial biopsy to treatment was 6.0 weeks, with 5 outliers experiencing an interval > 6 months. Seventy-three patients initiated ABVD, and 54 (74%) of these completed all 6 cycles. Treatment delays were common: 48 (66%) experienced at least 1 delay. Reasons for delays are listed in Table 2. Dose reductions were rare. Median dose intensity averaged across the 4 drugs was ≥ 85% in most (75%) patients.

The patient flow diagram is shown in Figure 2. Eight (11%) of 73 treated patients had primary refractory disease. Of those who completed therapy, at least 36 (67%) achieved a complete response by physical examination. Nineteen patients (26%) discontinued therapy, several for unknown reasons (n = 10) or death (n = 6). Of the 6 deaths while on treatment, 4 occurred within 14 days of the first dose of ABVD. On the basis of available information, these 4 patients had end-stage disease at the time they started ABVD. Three patients experienced relapse 5.1, 5.6, and 20.0 months after treatment. Additional patients known to have died may have experienced relapse but had not sought care at BCCOE. At the time of analysis, 33 patients (43%) are in clinical remission, 27 (36%) are deceased or were referred to hospice, and 17 (22%) were lost to follow-up, with a 3-year survival estimate of 63% (95% CI, 50% to 74%). The median duration of follow-up was 1.7 years (maximum, 7.4 years). Survival data are shown in Figure 3.

Univariable analysis with Kaplan-Meier survival estimation and log-rank testing demonstrates that worse ECOG performance status ($P < .01$), advanced stage ($P < .01$), B symptoms ($P < .01$), anemia ($P \leq .01$), failure to complete treatment ($P \leq .01$), and dose intensity < 85% ($P < .01$) were associated with worse survival, as shown in Figure 4. The 3-year survival estimate for patients with low dose intensity was 36% (95% CI, 12% to 61%) *v* 73% (95% CI, 56% to 84%) for high dose intensity. Several variables were not statistically significant, including age, sex, HIV status, bulky disease, lymphopenia, histologic subtype, and EBV status.

DISCUSSION

Before the establishment of BCCOE in 2012, most patients with HL in Rwanda, as in many low-income countries, died as a result of their disease. Death that results from an untreated, and often undiagnosed, yet highly curable malignancy is a social injustice in the current era of unprecedented breakthroughs, cure rates, and profits in the field of oncology.[10-12] To begin to close the vast outcome gaps in cancer mortality between rich and poor countries, effective cancer care delivery systems must be built and iteratively improved. An implementation science approach to oncology capacity building, in which strategies for effective care delivery are continuously evaluated through assessment of both quality indicators and clinical outcomes, optimizes the chance of success and sustainability.[16-18] Here, we illustrate this approach through our experience in developing the capacity to treat and cure HL in rural Rwanda.

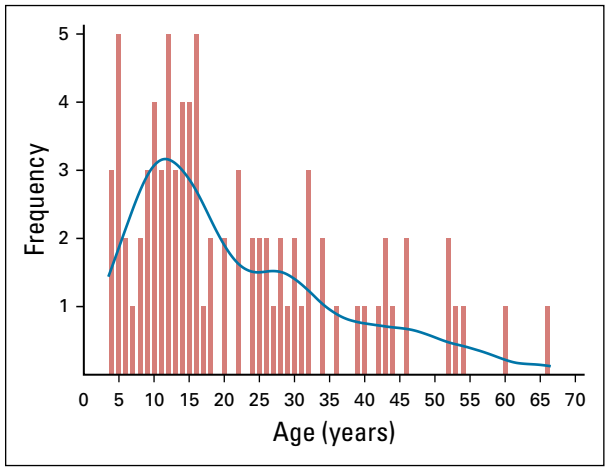

FIG 1. Age distribution (N = 85).

Nearly half of the patients in our cohort and the majority of those who completed treatment are in clinical remission, with a 3-year survival estimate of 63%. While longer follow-up is necessary, these results suggest that HL can be successfully treated in a low-resource setting through implementation of a basic cancer care delivery system. Our patients in remission have a meaningful chance of living normal, healthy lives, whereas a decade ago, they would have likely died as a result of untreated disease. Despite this tremendous progress, we are only halfway to our goal of achieving equity for patients with HL in Rwanda. Our treatment outcomes are inferior to similarly treated patients from HICs, and 30% of our cohort either did not start or did not complete treatment.

Examination of quality indicators can facilitate targeted improvement within a care delivery system. A quality indicator is a measurable element of practice performance for which there is evidence or consensus that it can be used to assess the quality of care provided.[19] Quality indicators have been developed for non-HL[20] and proposed for early-stage HL with an emphasis on radiotherapy,[21] but there are no well-established quality indicators for medical management of HL. We based our assessment here on adherence to the nationally endorsed protocol adapted from evidence-based guidelines and benchmarks extrapolated from other available sources.

TABLE 2. Quality Indicators (n = 77)

Quality Indicator	No. (%)
Pathologic diagnosis	
Final pathologic diagnosis determined by	
Fine needle aspiration only	1 (1)
Biopsy with histology	29 (38)
Biopsy with histology and immunohistochemistry	47 (61)
Source of final pathology result	
Butaro Cancer Center of Excellence	32 (42)
Brigham and Women's Hospital	19 (25)
University Teaching Hospital of Kigali	12 (16)
King Faisal Hospital	6 (8)
University Teaching Hospital of Butare	4 (5)
Rwanda Military Hospital	1 (1)
Other	3 (4)
Staging evaluation[a]	
Chest x-ray	66 (86)
Abdominal ultrasound	27 (35)
CT scan of chest, abdomen, and/or pelvis	14 (18)
No imaging obtained	7 (9)
Bone marrow aspiration and biopsy	17 (22)
Treatment quality indicators	
Median time from initial biopsy to C1D1 ABVD, weeks (IQR)	6.0 (3.4-10.9)
Median time to completion of ABVD, weeks (IQR)	26.1 (25.0-28.1)
Reason for treatment delays (n = 117 total delays)[a]	
Neutropenia	37 (32)
Social factors	16 (14)
Infection (confirmed or suspected)	9 (8)
Thrombocytopenia	6 (5)
Stockout	3 (3)
Scheduled	3 (3)
Elevated liver enzymes	3 (3)
Other	19 (16)
Not documented	21 (18)
Dose intensity of ABVD across all completed cycles, %[b]	
Mean (SD)	89 (13)
Median (IQR)	92 (85-99)
Frequency of ABVD dose intensity, %	
< 85 across all completed cycles	18 (25)
85-97 across all completed cycles	32 (44)
> 97 across all completed cycles	23 (32)

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; C1D1, cycle 1 day 1; CT, computed tomography; IQR, interquartile range; SD, standard deviation.

[a]Answers were not mutually exclusive; percentages do not add up to 100.

[b]Dose intensity (or dose per unit time) = standardized dose/standardized time, where standardized dose = documented dose given/expected protocol-specified dose and standardized time = observed duration/expected duration.[14]

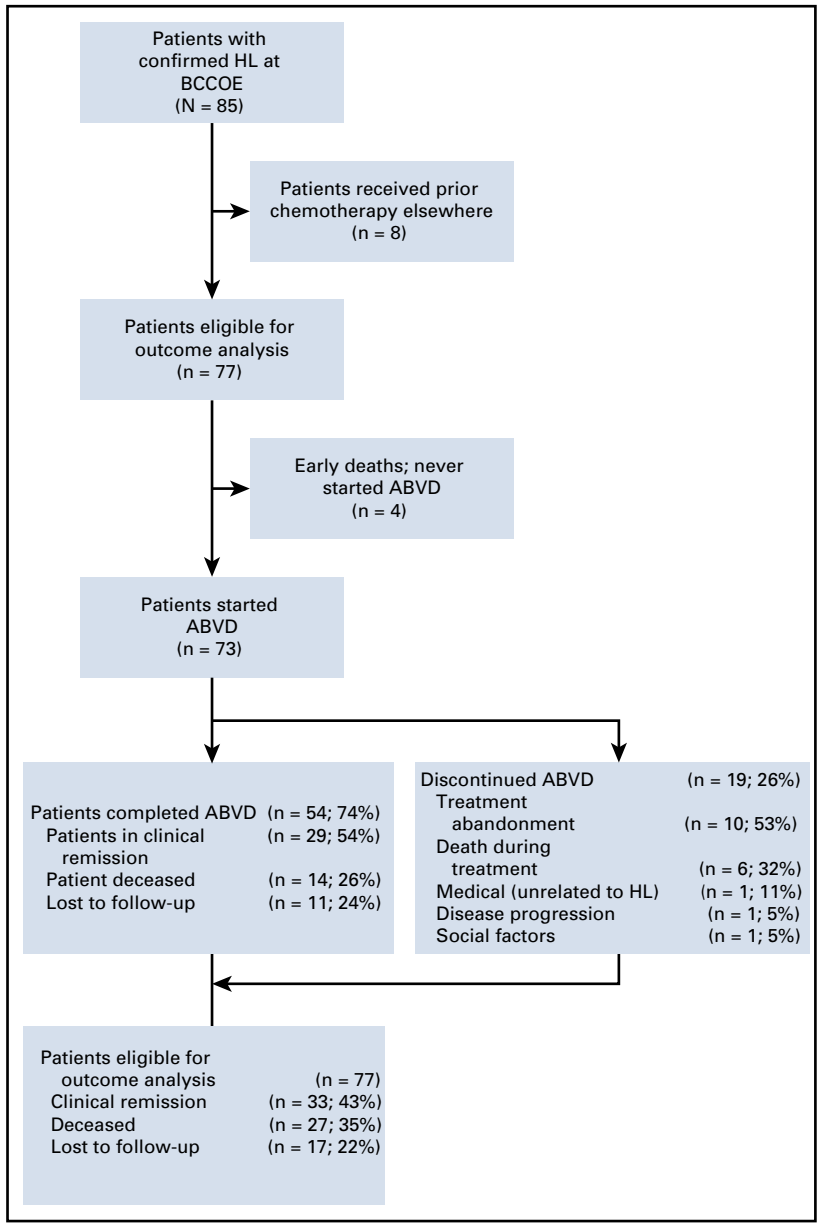

FIG 2. Patient flow diagram. ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; BCCOE, Butaro Cancer Center of Excellence; HL, Hodgkin lymphoma.

In our cohort, all patients except 1 were diagnosed by histologic examination of an excisional or core needle lymph node biopsy. Pathology capacity grew substantially at BCCOE, and in Rwanda, during the study period, from a starting point of relying on shipping specimens to the United States for diagnosis to having a pathologist permanently based at BCCOE who can consult telepathology as needed.[13] As capacity has evolved, the turnaround time from initial biopsy to final diagnosis has shortened.[22] Access to high-quality CT imaging and reports has also improved over time, and our patients with lymphoma are increasingly staged by CT, although positron emission tomography remains unavailable. With the recent establishment of radiotherapy in Rwanda, complete staging now affects HL management decisions and has been upgraded to a requirement in our protocol. Radiographic response measurement is considered a quality indicator for non-HL[20] and should be a target for capacity building as access to imaging and consolidative or second-line therapy expands.

By several indicators, clinical management of patients with HL at BCCOE may be considered high quality. All treatment candidates received ABVD with rare deviations; 4 patients received a single substitution of cyclophosphamide, doxorubicin, vincristine, and prednisone during a 2-week bleomycin stockout. The median duration of ABVD treatment was only 2 weeks longer than planned, and most of our patients received at least 85% dose intensity, with approximately one third receiving $> 97\%$. In contrast to other reports,[14] higher dose intensity was associated with better survival, representing another potential target for quality improvement.

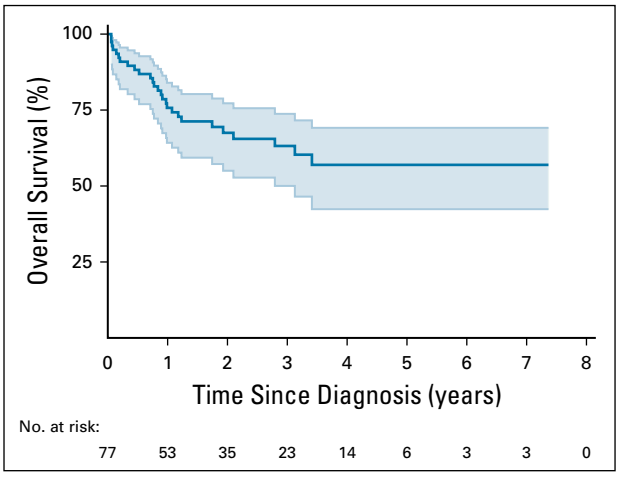

FIG 3. Kaplan-Meier overall survival estimate (n = 77).

Nevertheless, delays remain a challenge in our setting. Quality indicators for non-HL recommend a diagnostic period of 3 weeks after initial presentation, with therapy starting within 2 weeks of diagnosis.[20] While dates of initial outside presentation were not available for our cohort, we know that there are often significant delays in diagnosis. The median interval from initial biopsy to treatment was 6 weeks, with several outliers taking much longer. This interval comprises many targets for intervention: initial presentation to biopsy, pathology turnaround time at referring institutions, time from outside referral to BCCOE intake, turnaround time for pathology review or repeat biopsy at BCCOE, and time from final diagnosis to treatment start. Targeting these variables will require strategies to address barriers at multiple levels: training primary care providers, adequately staffing and stocking pathology laboratories, streamlining interinstitutional coordination, and mitigating the travel burden and costs incurred by patients.

Delays during treatment are also an opportunity for improvement. Many delays were due to neutropenia, even though the protocol recommends starting treatment with asymptomatic neutropenia. This discrepancy may be due to inconsistent protocol adherence or greater caution in a population with difficulty accessing care and a limited sepsis management infrastructure. Social factors, including inability to pay bus fare to BCCOE and opportunity costs for patients and families of missing income or school, were also significant. While PIH subsidizes costs for many patients, financial burdens remain a significant barrier. Controllable factors, such as chemotherapy stockouts and accommodations for holidays, were also appreciated. Education and reinforcement of the importance of timely therapy for both patients and providers warrant ongoing deliberate effort. Finally, treatment abandonment and loss to follow-up are key targets in our setting. Social and financial barriers are implicated for many who discontinued treatment. Better interventions to overcome the barriers that threaten curative therapy are needed, such as financial subsidies, psychosocial support, education of and coordination with local primary care providers, and reduction of stigma associated with cancer through public awareness and advocacy.

The disparity in outcomes between cohorts from HICs and ours may also be due to disease factors. The strongest signal of a potential biologic difference is the strikingly younger age distribution compared with HICs. Half of our patients were age $<$ 16 years, whereas we saw very few cases in older adults. This trend contrasts sharply with the well-described bimodal age distribution in HICs characterized by an initial peak of approximately 26 years and a late peak of approximately 65 years. Others have described an earlier peak in childhood in LMICs[23] and hypothesized that HL is seen in younger children in Africa because of earlier acquisition of EBV.[8,24]

The association between EBV and HL is well established,[25] and prevalence of EBV positivity in patients with HL is highest in Africa (74.2%) compared with all other regions.[26] In our study, EBV positivity was 67%, although the numbers were small. HIV is also associated with an elevated risk of HL, likely caused by loss of immunologic control of EBV. Overall, HIV-related HL is associated with advanced stage at presentation, unusual sites of disease, and poorer outcomes.[27] HIV prevalence among patients with lymphoma in sub-Saharan Africa ranges from 30% to 70%.[1] Only 12% of our patients were HIV positive, but HIV prevalence in Rwanda generally is 3%, lower than in the sources of these estimates.[28]

Clinically, a majority of our patients presented with advanced stage, B symptoms, and anemia, established poor prognostic factors that were also associated with worse survival in our analysis. Moreover, because complete staging was rarely performed, stage was very likely underestimated. Four patients died as a result of their disease without ever starting treatment, and 6 more died before completing treatment, with 4 after only 1 dose. While adverse clinical features may be due to delayed diagnosis, they may also reflect more aggressive underlying disease.

As a retrospective chart review, data quality was limited by the lack of systematic clinical assessments. Documentation also was missing clinical information.

In conclusion, we have demonstrated that with attention to implementation of quality care, many patients with HL can be successfully treated in a low-resource setting, although results remain inferior to those of HICs. We aspire to an equitable landscape in oncology globally, where patients in Rwanda and other LMICs have access to the highest quality of care. As a first step, we advocate for implementation of cancer care delivery systems, such as the one described here, with ongoing evaluation and efforts toward improvement. Ultimately, mechanisms for early diagnosis and therapy, in addition to availability of autologous stem-cell transplantation and novel anticancer agents, will be needed to raise the level of treatment success in LMICs to those seen in an HIC.

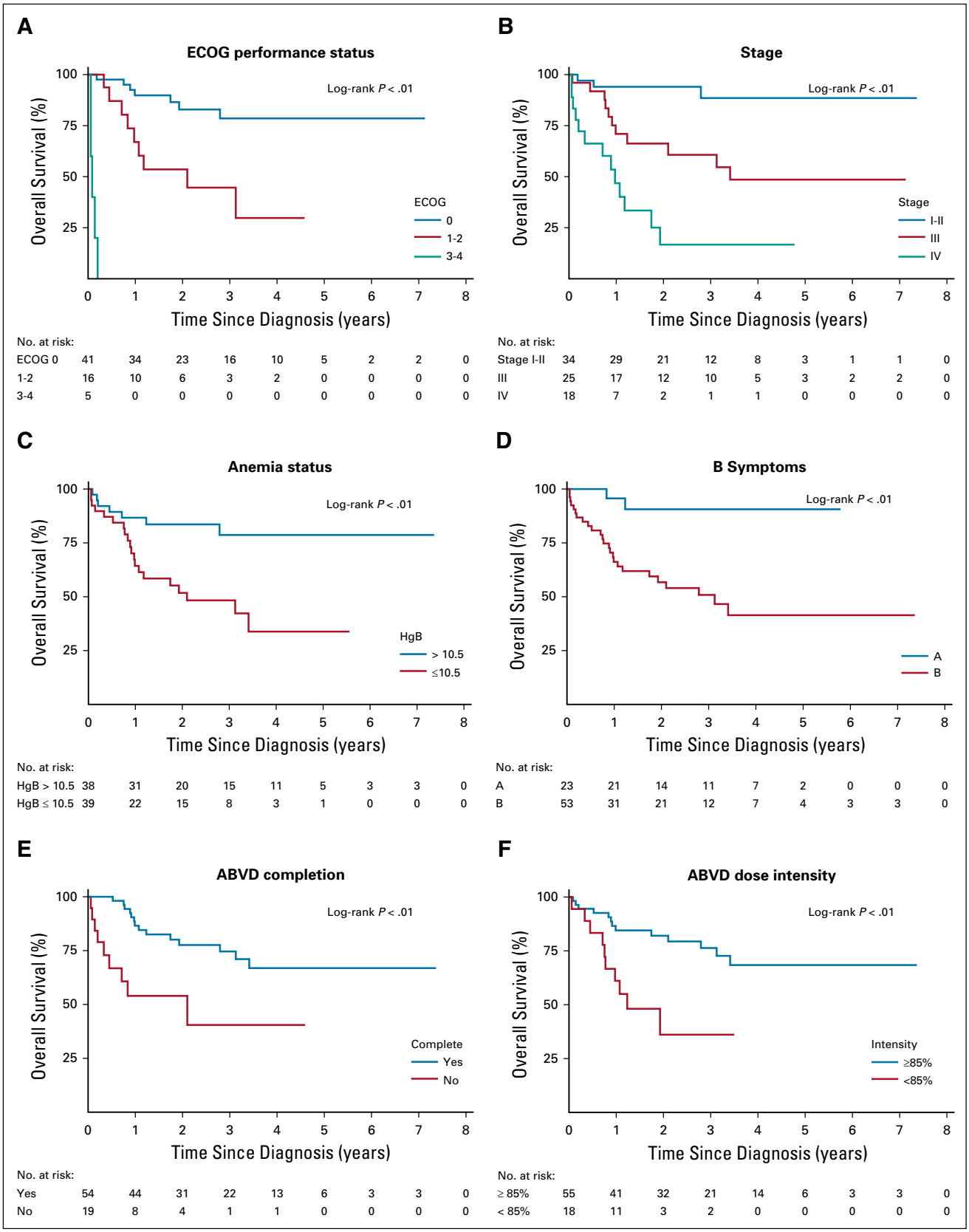

FIG 4. Kaplan-Meier overall survival estimates by prognostic factors (n = 77). Estimated overall survival by (A) Eastern Cooperative Oncology Group (ECOG) performance status (available in n = 62), (B) Ann Arbor stage, (C) anemia status, (D) B symptoms (available in n = 76), (E) doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) completion, and (F) ABVD dose intensity. HgB, hemoglobin.

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PRIOR PRESENTATION

Presented at the 61st American Society for Hematology Annual Meeting & Exposition, Orlando, FL, December 7-10, 2019.

SUPPORT

R.J.D. was supported by the Fogarty International Center and the National Cancer Institute of the National Institutes of Health under award no.D43TW009343, the Global Cancer Program at UCSF Helen Diller Family Comprehensive Cancer Center, and the University of California Global Health Institute. The content is solely the responsibility of the authors and does not necessarily represent the official views of the funding sources. The funding sources were not involved in the design of the study; collection, analysis, and interpretation of data; or writing of the manuscript.

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Financial support: Lawrence N. Shulman
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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Temidayo A. Fadelu
Research Funding: Celgene (Inst), Cepheid (Inst)

Lawrence N. Shulman
Research Funding: Celgene

No other potential conflicts of interest were reported.

REFERENCES

1. Gopal S, Wood WA, Lee SJ, et al: Meeting the challenge of hematologic malignancies in sub-Saharan Africa. Blood 119:5078-5087, 2012
2. Global Cancer Observatory: Homepage. http://gco.iarc.fr
3. Canellos GP, Rosenberg SA, Friedberg JW, et al: Treatment of Hodgkin lymphoma: A 50-year perspective. J Clin Oncol 32:163-168, 2014
4. Meyer RM, Gospodarowicz MK, Connors JM, et al: ABVD alone versus radiation-based therapy in limited-stage Hodgkin's lymphoma. N Engl J Med 366:399-408, 2012
5. Canellos GP, Anderson JR, Propert KJ, et al: Chemotherapy of advanced Hodgkin's disease with MOPP, ABVD, or MOPP alternating with ABVD. N Engl J Med 327:1478-1484, 1992
6. Duggan DB, Petroni GR, Johnson JL, et al: Randomized comparison of ABVD and MOPP/ABV hybrid for the treatment of advanced Hodgkin's disease: Report of an intergroup trial. J Clin Oncol 21:607-614, 2003
7. Shulman LN, Wagner CM, Barr R, et al: Proposing essential medicines to treat cancer: Methodologies, processes, and outcomes. J Clin Oncol 34:69-75, 2016
8. Stefan DC: Hodgkin lymphoma in Africa: Present and future. Transfus Apheresis Sci 49:144-146, 2013
9. Stulac S, Binagwaho A, Tapela NM, et al: Capacity building for oncology programmes in sub-Saharan Africa: The Rwanda experience. Lancet Oncol 16:e405-e413, 2015
10. Gyawali B, Sullivan R, Booth CM: Cancer groundshot: Going global before going to the moon. Lancet Oncol 19:288-290, 2018
11. Gopal S: Moonshot to Malawi. N Engl J Med 374:1604-1605, 2016
12. Farmer P, Frenk J, Knaul FM, et al: Expansion of cancer care and control in countries of low and middle income: A call to action. Lancet 376:1186-1193, 2010
13. Mpunga T, Hedt-Gauthier BL, Tapela N, et al: Implementation and validation of telepathology triage at cancer referral center in rural Rwanda. J Glob Oncol 2:76-82, 2016

13a. Rubagumya F, Greenberg L, Manirakiza A, et al: Increasing global access to cancer care: models of care with non-oncologists as primary providers. Lancet Oncol 18:1000-1002, 2017

14. Owadally WS, Sydes MR, Radford JA, et al: Initial dose intensity has limited impact on the outcome of ABVD chemotherapy for advanced Hodgkin lymphoma (HL): Data from UKLG LY09 (ISRCTN97144519). Ann Oncol 21:568-573, 2010

15. Hasenclever D, Diehl V: A prognostic score for advanced Hodgkin's disease. International Prognostic Factors project on advanced Hodgkin's disease. N Engl J Med 339:1506-1514, 1998
16. DeBoer RJ, Ndumbalo J, Meena S, et al: Development of a theory-driven implementation strategy for cancer management guidelines in sub-Saharan Africa. Implement Sci Commun 1:24, 2020
17. Koczwara B, Birken SA, Perry CK, et al: How context matters: A dissemination and implementation primer for global oncologists. J Glob Oncol 2:51-55, 2016
18. Tapela NM, Mpunga T, Karema N, et al: Implementation science for global oncology: The imperative to evaluate the safety and efficacy of cancer care delivery. J Clin Oncol 34:43-52, 2016
19. Lawrence M, Olesen F: Indicators of quality in health care. Eur J Gen Pract 3:103-108, 1997
20. Wennekes L, Ottevanger PB, Raemaekers JM, et al: Development and measurement of guideline-based indicators for patients with non-Hodgkin's lymphoma. J Clin Oncol 29:1436-1444, 2011
21. Roos DE, Tee HC: Quality indicators for early stage Hodgkin's lymphoma. J Med Imaging Radiat Oncol 61:550-556, 2017
22. Muvugabigwi G, Nshimiyimana I, Greenberg L, et al: Decreasing histology turnaround time through stepwise innovation and capacity building in Rwanda. J Glob Oncol 10.1200/JGO.17.00081
23. Thomas RK, Re D, Zander T, et al: Epidemiology and etiology of Hodgkin's lymphoma. Ann Oncol 13:147-152, 2002
24. Sherief LM, Elsafy UR, Abdelkhalek ER, et al: Hodgkin lymphoma in childhood: Clinicopathological features and therapy outcome at 2 centers from a developing country. Medicine (Baltimore) 94:e670, 2015
25. Thorley-Lawson DA, Gross A: Persistence of the Epstein-Barr virus and the origins of associated lymphomas. N Engl J Med 350:1328-1337, 2004
26. Lee J-H, Kim Y, Choi J-W, et al: Prevalence and prognostic significance of Epstein-Barr virus infection in classical Hodgkin's lymphoma: A meta-analysis. Arch Med Res 45:417-431, 2014
27. Dolcetti R, Boiocchi M, Gloghini A, et al: Pathogenetic and histogenetic features of HIV-associated Hodgkin's disease. Eur J Cancer 37:1276-1287, 2001
28. Ministry of Health, Republic of Rwanda: National HIV Annual Report: 2013-2014. http://www.rbc.gov.rw/IMG/pdf/national_hiv_annual_report_2013_2014_final_august_15_2014_2_.pdf

