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RESEARCH ARTICLE

Improved survival of children and adolescents with classical Hodgkin lymphoma treated on a harmonised protocol in South Africa

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Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ABVD–ChlVPP, doxorubicin, bleomycin, vinblastine, dacarbazine–chlorambucil, vinblastine, prednisone and procarbazine; ATR, adapted treatment regimen; CHIPS, Childhood Hodgkin International Prognostic Score; COPDac, cyclophosphamide, vincristine, prednisone, dacarbazine; CT, computed tomography; DS, Deauville score; GICC, Global Initiative for Childhood Cancer; HIC, high-income country; HIV, human immunodeficiency virus; HL, Hodgkin lymphoma; LMIC, low- and middle-income country; OPPA/OEPA–COPP, vincristine, procarbazine/etoposide, prednisone and doxorubicin; OS, overall survival; PET-CT, positron emission tomography-computed tomography; PI, principal investigator; POU, paediatric oncology unit; RER, rapid early response; SER, slow early response.

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Abstract

Background: Historic South African 5-year overall survival (OS) rates for Hodgkin lymphoma (HL) from 2000 to 2010 were 46% and 84% for human immunodeficiency virus (HIV)-positive and HIV-negative children, respectively. We investigated whether a harmonised treatment protocol using risk stratification and response-adapted therapy could increase the OS of childhood and adolescent HL.

Methods: Seventeen units prospectively enrolled patients less than 18 years, newly diagnosed with classical HL onto a risk-stratified, response-adapted treatment protocol from July 2016 to December 2022. Low- and intermediate-risk patients received four and six courses of adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD), respectively. High-risk patients received two courses of ABVD, followed by four courses of cyclophosphamide, vincristine, prednisone, and dacarbazine (COPDac). Those with a slow early response and bulky disease received consolidation radiotherapy. HIV-positive patients could receive granulocyte colony-stimulating factor and less intensive therapy if stratified as high risk, at the treating clinician's discretion. Kaplan–Meier survival analysis was performed to determine 2-year OS and Cox regression to elucidate prognostic factors.

Results: The cohort comprised 132 patients (19 HIV-positive, 113 HIV-negative), median age of 9.7 years, with a median follow-up of 2.2 years. Risk grouping comprised nine (7%) low risk, 36 (27%) intermediate risk and 87 (66%) high risk, with 71 (54%) rapid early responders and 45 (34%) slow early responders, and 16 (12%) undocumented. Two-year OS was 100% for low-risk, 93% for intermediate-risk, and 91% for high-risk patients. OS for HIV-negative (93%) and HIV-positive (89%) patients were similar ($p = .53$). Absolute lymphocyte count greater than 0.6×10^9 predicted survival (94% vs. 83%, $p = .02$).

Conclusion: In the first South African harmonised HL treatment protocol, risk stratification correlated with prognosis. Two-year OS of HIV-positive and HIV-negative patients improved since 2010, partially ascribed to standardised treatment and increased supportive care. This improved survival strengthens the harmonisation movement and gives hope that South Africa will achieve the WHO Global Initiative for Childhood Cancer goals.

KEYWORDS
adolescent, child, GICC, harmonisation, Hodgkin lymphoma, South Africa

1 | INTRODUCTION

Retrospective reports have documented relatively high survival rates for paediatric Hodgkin lymphoma (HL) with 85% 3-year overall survival (OS) in Morocco[1] and 96% 5-year OS in Egypt,[2] both lower middle-income countries. There are minimal prospective data on HL survival in Africa, and hardly any data on children with human immunodeficiency virus (HIV). Standardised HL guidelines have been shown to improve survival.[3] However, these guidelines are frequently used without adaptation in low- and middle-income countries (LMIC) despite being created for use in high-income countries (HIC) with adequate access to excellent supportive care, and various salvage therapy options, such as antibody–drug conjugates, checkpoint inhibitors and stem cell transplantation.

The WHO Global Initiative for Childhood Cancer (GICC) focuses on six index cancers, including HL.[4] In 2014, the South African Children's Cancer Study Group (SACCSG) initiated a process to harmonise diagnostic and treatment guidelines for childhood cancers, starting with HL. Prior to this initiative, risk grouping was not widely applied, and response-adapted therapy was not widely practised. A multicentre, retrospective study documented that the 5-year OS rates for children with HL were low at 46% for those

with HIV, compared to 84% for those without, and that treatment with doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) yielded higher survival rates than vincristine, procarbazine/etoposide, prednisone and doxorubicin–cyclophosphamide, vincristine, prednisone, procarbazine (OPPA/OEPA–COPP) and adriamycin, bleomycin, vincristine and dacarbazine–chlorambucil, vinblastine, prednisone and procarbazine (ABVD–ChlVPP). The strongest prognosticators were HIV infection and advanced disease, thus informing the treatment choices for patients in the prospective treatment protocol.[5]

The current prospective study aimed to determine if a harmonised treatment protocol incorporating risk stratification and response adjustment, representing an adapted treatment regimen (ATR) for an upper middle-income country, was associated with improved survival, and to further evaluate potential prognostic markers of survival.

2 | METHODS

2.1 | Setting

South Africa, an upper middle-income country, has a high rate of unemployment, the highest number of HIV-positive people in the world and sustained inequity, with a documented childhood cancer OS of approximately 60%.[6,7] Patients are treated in 12 state-sector academic hospitals and five private-sector hospitals. State hospitals provide subsidised treatment based on means assessment. Patients under 6 years, refugees, those receiving state financial grants and those with no income were fully subsidised by the state (H0). Three higher levels of income classification (H1–H3) reflected varying degrees of state subsidisation, while foreign nationals who did not have official refugee status and patients with medical insurance were grouped in the highest income classification (private) with no subsidisation.[8]

2.2 | Inclusion and exclusion criteria

This multicentre, prospective, observational study included newly diagnosed, treatment-naïve patients under 18 years with histologically confirmed classical HL diagnosed and treated in South Africa from July 2016 to December 2022. Exclusion criteria included nodular lymphocyte-predominant HL, previous treatment for HL, those who died before treatment was initiated and those with substantively incomplete data collection.

2.3 | Staging and imaging

Patients were staged according to the Ann Arbor classification system and risk-stratified into low, intermediate or high risk (Table S1). This risk stratification was based on various treatment algorithms in use[3] and was intended to ensure that children with HL in South Africa receive appropriate treatment.

Staging investigations included chest x-ray, fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT), or computed tomography when PET-CT not available and bone marrow trephine biopsy for all patients. Bulky disease was defined as peripheral lymph nodes or lymph node aggregates greater than 6 cm in any axis, or mediastinal adenopathy greater than 33% of the thoracic diameter in an anteroposterior chest radiograph. Central review of PET-CT was performed as requested. Laboratory investigations included haematological (total white cell count, absolute lymphocyte count (ALC), absolute eosinophil count, haemoglobin), non-specific markers (ferritin, lactate dehydrogenase [LDH], albumin, erythrocyte sedimentation rate [ESR]) and HIV status. Pre-treatment echocardiograms were performed according to availability.

2.4 | Intervention

Patients were enrolled in a risk-stratified, response-adapted protocol comprising two cycles of ABVD for all patients, followed by interim assessment. Based on treatment response, further treatment included: two further cycles of ABVD for low-risk patients, four cycles of ABVD for intermediate-risk patients and four cycles of COPDac (cyclophosphamide, vincristine, prednisone, dacarbazine) for high-risk patients.[9]

2.5 | Definitions of response

Response evaluation was based on the 2015 revised Lugano classification,[10] and was determined at response evaluation after two to three cycles of ABVD. In patients who did not have PET-CT performed, CT was considered sufficient. Rapid early response (RER) was defined as complete resolution (CR) of measurable disease and resolution of PET avidity, that is, Deauville score (DS) 1, 2 or 3 or a good partial response (GPR) with a reduction of 50% or greater in any one axis of a measurable nodal mass with a DS of 1–3.[11]

Slow early response (SER) was defined as a partial response (PR) with shrinkage of measurable disease not achieving 50% reduction in any one axis or DS 4 or 5. Progressive disease (PD) was defined as increased intensity of FDG uptake on the PET-CT from baseline, any increase in any one axis of a measurable nodal mass and/or new lesions. Stable (refractory) disease was defined as DS 4 or 5, or less than 50% decrease from baseline in the sum of the product of the perpendicular diameters (SPD) for multiple lesions of up to six dominant measurable nodes and extranodal sites.[11] Progressive disease was defined as DS of 4 or 5 with increased intensity from baseline, increase by 50% or higher size from the nadir, or significantly increased, new, or recurrent splenomegaly with focal lesions on available radiology images.

2.6 | Permitted protocol modifications

HIV-positive patients could receive additional support with granulocyte colony-stimulating factor, and could be treated on less intensive therapy (intermediate risk instead of high risk), at the treating clinician's discretion. Patients with pre-existing cardiac dysfunction (ejection fraction of <50%) could be treated with COPDac instead of ABVD upfront, have doxorubicin omitted or epidoxorubicin substituted for doxorubicin if available, at the discretion of the treating clinical team.

2.7 | Consolidation with radiotherapy

Radiotherapy was limited to those sites in which functional activity (DS 4 to 5) was appreciable at response evaluation and for mediastinal masses greater than 33% of the intrathoracic diameter at presentation, regardless of the response evaluation. Bulky disease outside the mediastinum at presentation did not mandate radiation, if there was no FDG uptake on the interim PET-CT scan (DS 1–3). For patients who did not have PET-CT, only mediastinal sites and nodal masses classified as SER with a partial response as defined above were irradiated. Involved site radiotherapy utilising three-dimensional conformal radiotherapy planning or involved field radiation was administered according to institutional capacity at a dose of 21–25 Gy, in either 1.5 or 1.8 Gy fractions.

2.8 | Statistics

The primary study endpoints were 2-year progression-free survival (PFS) and OS. OS was defined as time from diagnosis to death from any cause. PFS was defined as time from diagnosis to date of confirmation of relapsed or refractory disease. Persistent disease identified within 90 days of completion of therapy was deemed refractory; disease that returned more than 90 days after therapy was classified as early relapse if within 12 months from the end of therapy, and late relapse if thereafter. Patients who did not experience an event were censored at the date of the last follow-up.

Data were entered prospectively into a central REDCap[12] database by one clinician-researcher from each paediatric oncology unit (POU), and the principal investigator (PI) managed the entire database. Data were frozen on 31 December 2022. The Kaplan–Meier method and log-rank test were used to calculate survival analysis. A Cox proportional hazards model was used for univariate analysis to identify predictive factors for OS. Potential prognostic factors included demographic (age, sex, maternal education and hospital-assigned financial classification), disease-specific (HIV infection, histological subtype, B symptoms, mediastinal mass, pleural effusion, stage, risk group), haematological (total white cell count, ALC, total eosinophil count, haemoglobin), non-specific markers (LDH, ESR, ferritin, albumin) and Childhood Hodgkin International Prognostic Score (CHIPS).[13] These non-specific markers were evaluated in an attempt to find prognostic markers that are relatively cheap and widely available in South Africa. In the CHIPS score, one point was assigned for each of the four known predictors of adverse event-free survival (EFS): stage 4, large mediastinal mass, fever and albumin less than 35 g/dL.

Treatment abandonment was defined as failure to complete curative treatment, while loss to follow-up was defined as any patient who did not return for follow-up appointments for 1 year and was unreachable despite efforts to contact the family. Abandonment and loss to follow-up were censored in the survival curves. A *p*-value of less than .05 was considered statistically significant. The whole cohort was analysed together, and the HIV-uninfected patients were analysed separately to limit confounders.

2.9 | Ethics

The study was approved by the University of the Witwatersrand human research ethics committee (M1711100) and registered on the National Health Research Database and the seven Provincial Health Research Databases in which POUs were located. Approval was obtained from the ethics committee of each participating POU by the national PI.

3 | RESULTS

In total, 142 cases of HL were identified, of which 10 were excluded (Figure 1). The majority of patients ($n = 72$; 55%) were younger than 10 years of age. The median age at presentation in 113 (86%) HIV-negative patients was 9.7 years (range 2.3–18.7 years), and 9.1 years (range 4.8–18.2) in 19 (17%) HIV-positive patients, with a male predominance in both groups. The median follow-up time was 2.2 years (range: 0–7.5 years). Fifteen HIV-positive patients (79%) were already receiving antiretroviral therapy at the time of diagnosis of HL, and nine (60%) of these had undetectable viral loads. The majority ($n = 106$; 80%) received full or heavily subsidised care, and 16 (12%) patients were treated in the private sector (Table 1). The most common histological subtype was nodular sclerosing ($n = 67$; 51%), followed by mixed cellularity ($n = 38$; 29%). Histological subtype was not determined in 23 patients (17%), the majority, because these patients were too ill at presentation to undergo lymph node excision. Most patients presented with Ann Arbor stage 3 and 4 disease ($n = 87$; 66%), while 84 patients (64%) presented with B symptoms, 66 (50%) with bulky disease, and 40 (30%) patients with a mediastinal mass. The majority ($n = 87$; 66%) had high-risk disease, 36 (27%) had intermediate-risk disease and nine patients (7%) had low-risk disease. Demographic data and disease characteristics at diagnosis are shown in Table 1.

Ten patients (7.6%) presented with autoimmune manifestations including immune thrombocytopenia ($n = 2$; 1.5%), autoimmune

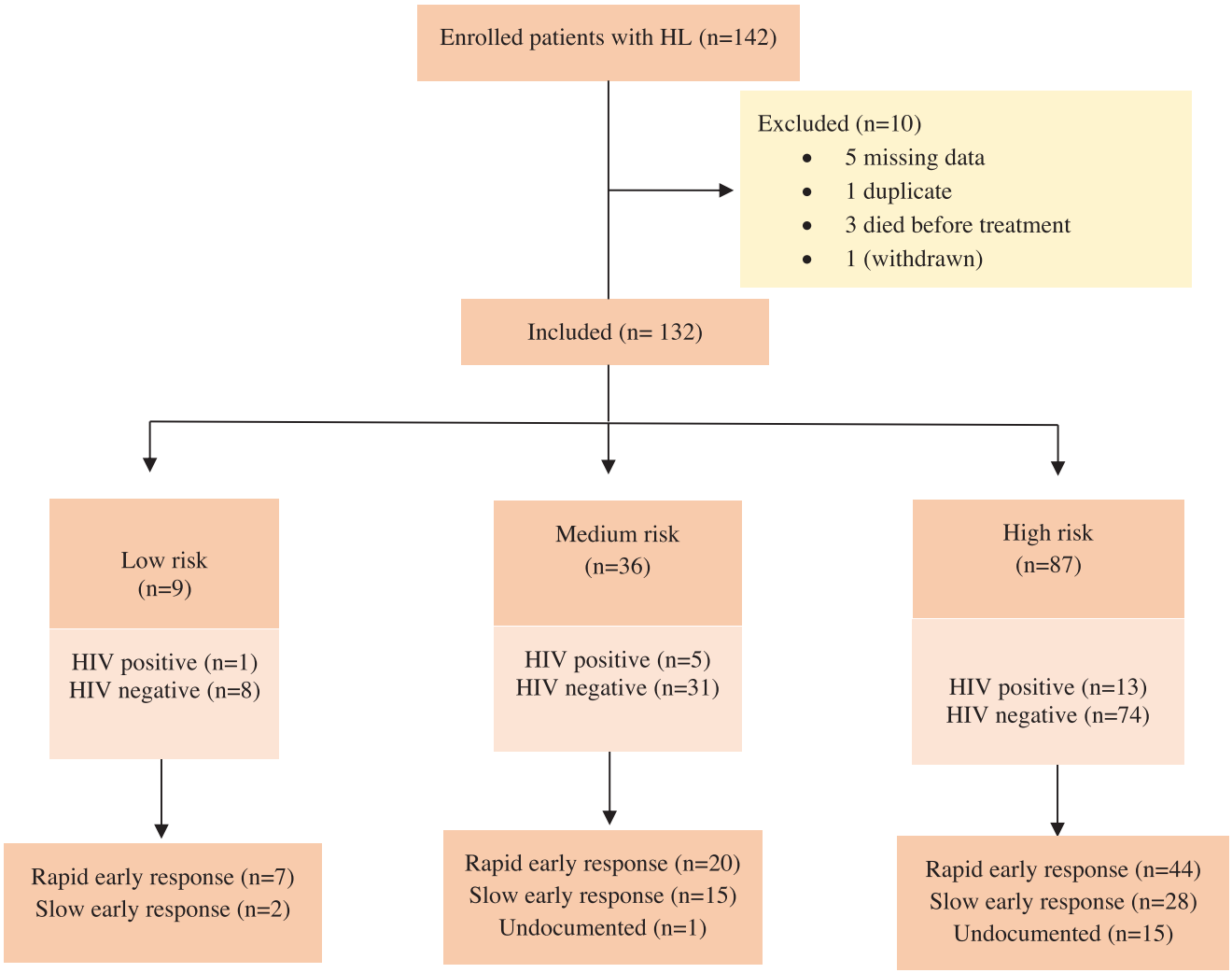

FIGURE 1 Enrolment, risk stratification and response assessment of children and adolescents on SACCSG (South African Childhood Cancer Study Group)-HL 2018.

haemolytic anaemia ($n = 7$; 5.3%), and Guillain–Barré syndrome ($n = 1$; 0.8%), while four (4.1%) HIV-negative patients of the 98 patients who had echocardiograms performed had cardiac dysfunction prior to starting therapy.

3.1 | Protocol deviations

Seven high-risk patients were undertreated (ABVD only instead of ABVD and COPDac), one intermediate-risk patient was overtreated (COPDac instead of ABVD) and three low-risk patients were overtreated (six cycles of ABVD instead of four).

3.2 | Response evaluation

Response evaluation was performed in 114 patients (86%): 104/114 (91%) with PET-CT scans and 10/114 (9%) with CT. Of 18 patients who did not have response evaluation performed, four died before reaching this point, four abandoned therapy, and two have not yet completed treatment. In six cases, no reason was documented. Seventy-three (65%) were classified as RER, 44 (39%) as SER and 15 were undocumented (see Figure 1).

3.3 | Radiation

Based on SER or the presence of bulky large mediastinal adenopathy at presentation, radiotherapy was indicated in 61 (46%) patients. Of these, 36 (59%) received radiation as mandated by the protocol. Reasons for omission included failure to adhere to the protocol due to poor understanding ($n = 11$), treatment abandonment ($n = 5$), refusal by the local radiation oncologist ($n = 3$), progressive disease with the decision to administer more chemotherapy ($n = 2$), inconclusive PET-CT results ($n = 2$), clinical judgement based on previous toxicity ($n = 1$) and death ($n = 1$).

TABLE 1 Patient characteristics and univariate analysis of potential prognostic factors.

	Variable	HIV (−) $n = 113$	%	HIV (+) $n = 19$	%	Total cohort $n = 132$	%	2-year OS	*p*-Value
Age	<10 years	50	56	17	89	72	55	92	.96
	>10 years	63	44	2	11	60	45	93	
Maternal education	Tertiary	18	16	0	0	18	14	100	.32
	School (any)	52	46	12	63	64	49	93	
	Undocumented	43	38	7	37	50	38	90	
Hospital financial classification	Private sector	15	13	1	5	16	12	100	.11
	H0, H1	81	72	0	0	99	75	94	
	H2, H3	17	15	18	95	17	13	78	
Histological subtype	Nodular sclerosing	58	51	9	47	67	51	90	.31
	Mixed cellularity	34	30	4	21	38	30	100	
	Lymphocyte depleted	2	2	0	0	2	1.5	100	
	Lymphocyte rich	2	2	0	0	2	1.5	100	
	NOS/undocumented	17	15	6	32	23	17	87	
EBER-ISH	Yes	41	36	4	21	47	36	93	.15
	No	25	19	6	32	31	23	100	
B symptoms	Present	72	64	12	63	84	64	93	.59
	Absent	41	36	7	3	48	36	92	
Ann Arbor stage	Stage 1	5	4	0	0	5	4	100	.45
	Stage 2	34	30	6	32	40	30	97	
	Stage 3	36	22	4	21	40	30	92	
	Stage 4	38	34	9	47	47	36	88	
Bulky disease (mediastinal and peripheral)	No	59	52	7	3	66	50	92	.69
	Yes	54	48	12	63	66	50	94	
Mediastinal mass ($n = 113$)	Yes	37		16	84	40	30	92	.88
	No	76	67	3	16	92	70	93	
Risk group	Low risk	8	7	1	5	9	7	100	.61
	Medium risk	31	27	5	26	36	27	94	
	High risk	74	66	13	68	87	66	91	
CHIPS	1	29	26	5	26	33	25	91	.64
	2	25	22	4	21	30	23	97	
	3	23	20	5	26	27	21	8	
	4	4	4	4	21	9	7	89	
	Undocumented	28	25	1	5	33	25	97	
Autoimmune manifestations	No	96	85	17	90	113	86	93	.1
	Yes	8	7	2	10	10	8	100	
	Undocumented	9	8	0	0	9	7	73	
Ferritin ($n = 114$)	<500 μg/L	59	62	9	47	68	60	97	.08
	>500 μg/L	37	39	9	47	46	40	88	

(Continues)

TABLE 1 (Continued)

Variable		HIV (–) $n = 113$	%	HIV (+) $n = 19$	%	Total cohort $n = 132$	%	2-year OS	*p*-Value
Lactate dehydrogenase ($n = 126$)	<500 μg/L	85	79	16	84	101	80	93	.57
	>500 μg/L	23	21	2	10	25	20	96	
Erythrocyte sedimentation rate	<30 mm/h	29	26	3	16	32	24	90	.65
	>30 mm/h	57	50	11	58	68	52	93	
	Undocumented	27	24	5	26	32	24	96	
Total white cell count	$<15 \times 10^9$/L	93	82	18	95	111	84	94	.13
	$>15 \times 10^9$/L	20	18	1	5	21	16	84	
Absolute lymphocyte count ($n = 130$)	$>0.6 \times 10^9$/L	107	96	15	79	122	94	94	.02
	$<0.6 \times 10^9$/L	5	4	3	16	8	6	75	
Absolute eosinophil count ($n = 130$)	$>0.6 \times 10^9$/L	16	14	2	10	18	14	100	.23
	$<0.6 \times 10^9$/L	96	86	16	84	112	86	91	
Haemoglobin	>10.5 g/dL	55	49	5	26	60	46	95	.44
	<10.5 g/dL	58	51	14	74	72	54	91	
Albumin ($n = 131$)	>35 g/L	50	44	7	37	57	44	96	.19
	<35 g/L	63	56	11	58	74	56	90	

Abbreviations: CHIPS, Childhood Hodgkin International Prognostic Score; EBER-ISH, Epstein–Barr virus-encoded RNA in situ hybridisation.

TABLE 2 Distribution of treatment failures.

	High risk		Medium-risk	
	HIV+	HIV–	HIV+	HIV–
Refractory or progressive disease ($n = 13$)				
Histological confirmation	0	4	0	0
No histological confirmation	1	6	0	2
Early relapse ($n = 3$)				
Histological confirmation	1	1	0	1
No histological confirmation	0	0	0	0
Late relapse ($n = 3$)				
Histological confirmation	0	2	0	0
No histological confirmation	0	1	0	0

3.4 | Treatment failure

Thirteen (9.8%) patients were identified as having refractory disease, four with histological confirmation, while six patients were diagnosed with relapsed disease, five histologically confirmed. None were low risk at presentation, and the majority were HIV-negative (see Table 2). The remainder were considered to have refractory disease based on end-of-treatment PET-CT scans, despite this assessment not being recommended in the study protocol. Therefore, the treatment failure rate was between 7% (proven) and 14% (total). Patients with relapsed or refractory disease were treated off-protocol according to institutional preference: eight patients received autologous stem cell transplants, and two were being prepared for transplant. At the last follow-up date, one patient had demised, six were alive in full remission and seven were alive with disease.

3.5 | Overall survival and progression-free survival

Causes of death included progression of disease ($n = 1$), relapse ($n = 1$), treatment-related mortality ($n = 6$) and other ($n = 1$). Five high-risk patients (4%) abandoned treatment after receiving two to four cycles

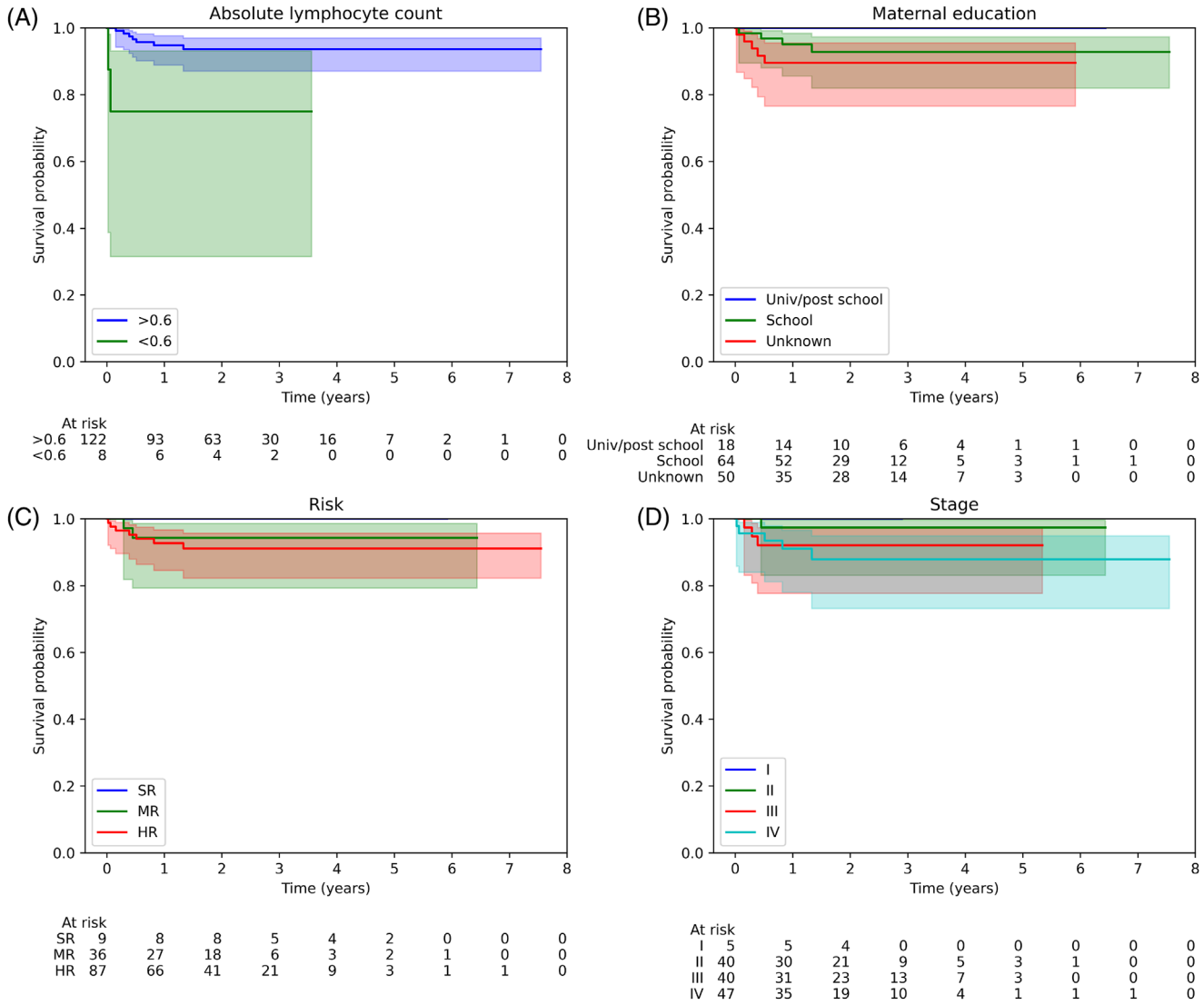

FIGURE 2 (A) Overall survival of current and historical cohort (B).

of chemotherapy, but were documented to be alive (47–941 days follow-up) despite not completing therapy.

The 2-year OS for the entire cohort was 92.6%, higher than that of the historical cohort, which was 84% (p = .004) (see Figure 2) with a PFS of 83%. HIV-negative patients had a 2-year OS of 93%, in comparison with 89% in the HIV-positive patients (p = .53). The 2-year OS was 100% for patients with stage 1 disease, 97% for stage 2, 92% for stage 3 and 88% for stage 4 (p = .45). The 2-year OS was 100% for low-risk, 94% for intermediate-risk, and 91% for high-risk patients (p = .62). The 2-year PFS for risk stratification was as follows: low risk 100%, intermediate risk 90% (95% confidence interval [CI]: 73%–79%) and high risk 79% (95% CI: 66%–87%).

Multiple factors were assessed for prognostic potential, and only ALC was found to be significant (p = .02, with wide CIs) (Table 1), although trends were observed (Figure 3). The 2-year OS for patients who received radiotherapy was 100%, in contrast with 89% in those who did not receive this treatment modality (p = .04, 95% CI: 80%–94%). The 2-year PFS was 93% in those who received radiotherapy and 79% in those who did not (p = .55, 95% CI: 67%–87%).

4 | DISCUSSION

In this prospective multicentre study, the 93% 2-year OS of paediatric patients with HL in South Africa is higher than the previous 87% 2-year OS reported in our earlier retrospective study, which had a 5-year OS of 79%.[5] This improvement may be ascribed to the use of a standardised protocol tailored to the local setting, with increased attention paid to supportive care. Most notably, the 2-year OS of patients with HIV and HL has dramatically risen from 65% in 2010[14] to 89%, nearly matching that of the HIV-negative patients. However, the 5-year OS of these patients in the retrospective cohort decreased to 44% due to ongoing opportunistic infections, and this cohort may also experience similar events.

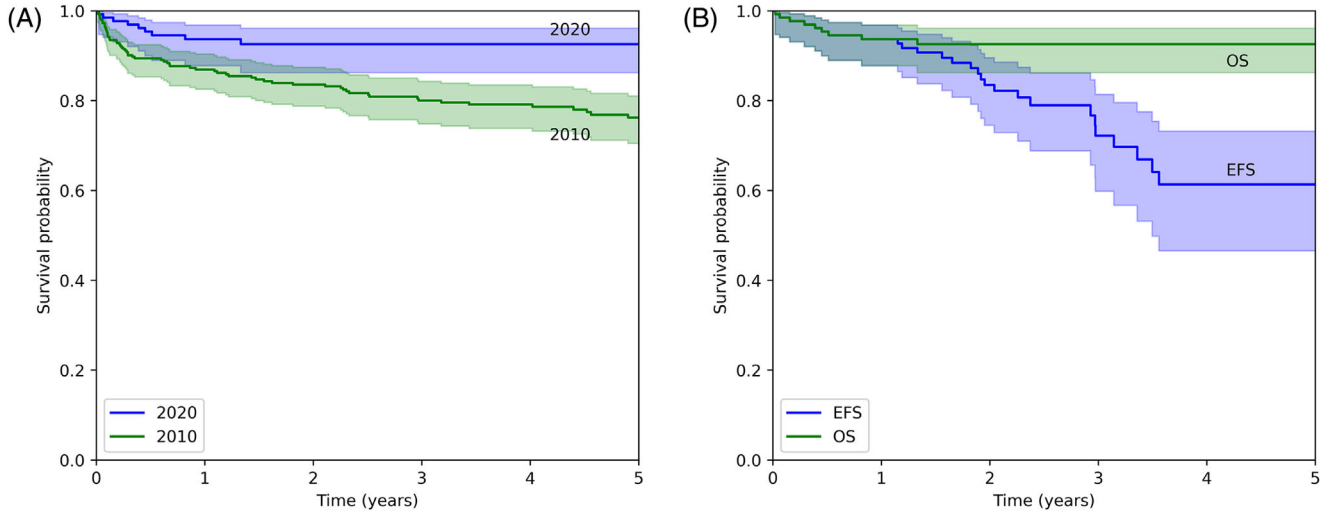

FIGURE 3 Kaplan–Meier survival curves for (A) absolute lymphocyte count (ALC), (B) materna.

The improved 2-year OS is more likely due to improved management of the treatment toxicity with better supportive care than choice of chemotherapy regimen. The analysis of the retrospective cohort, however, did reveal that treatment with ABVD rather than ABVD–ChlVPP or OEPA/OPPA–COPP was associated with less toxicity.[5]

The percentage of patients with HIV in this study (14%) is higher than that of the historical cohort (10%), while the rate of HIV infection in the general paediatric population has decreased over the same period.[15] This may reflect the phenomenon of an increasing incidence of HL in patients with HIV who survive longer nowadays, having evaded mortality from HIV-related opportunistic infections.

The improved 2-year OS and PFS may partially be ascribed to standardised treatment and increased supportive care, but may also reflect improved access to the healthcare system and changing demographic patterns. In contrast to our earlier study, HIV infection is no longer an adverse prognosticator, possibly reflecting increased competence in treating children with both HIV and HL or again reflecting the benefits of being treated according to standardised guidelines. It is also possible that decreased stigma and wider access to antiretroviral therapy contributed to this improvement. Children treated on randomised controlled trials are often shown to have good survival rates, although a definitive systematic review found no clear benefit, concluding that insufficient data exist to support this oft-quoted assertion.[16]

Although most potential prognostic factors were not shown to be statistically significant (Table 1), differences remain that may become significant with larger patient numbers (Figure 3). Alternatively, these results may suggest that adverse predictors may be largely overcome in patients receiving adequate multimodal therapy using risk stratification and response adaptation. This approach, more tailored to the individual patient, is relatively simple to implement[9] and achieves the goal of reserving radiotherapy for patients with SER disease, thus decreasing the number of patients at risk for radiotherapy-related late effects. The CHIPS score, shown to be predictive in intermediate-risk patients treated on doxorubicin hydrochloride, bleomycin, vincristine, etoposide, prednisone and cyclophosphamide (ABVE-PC),[13] was perhaps not predictive here, because the score does not accurately prognosticate in this population treated on a different regimen.

The rate of abandonment is relatively low, which we attribute to the means-based partial or complete subsidisation of medical care, as well as additional support from various non-governmental organisations. Despite abandoning therapy, these patients were documented to be alive, perhaps suggesting that decreased treatment intensity might be appropriate, but it must be noted that the period of follow-up is as yet too short to confirm this, and some patients may yet relapse. Nevertheless, further efforts should continue to address treatment abandonment.

Treatment-related mortality represented two-thirds of the deaths in contrast with 33% in the historical cohort, although again, the numbers in the current study are too low to make meaningful comparisons and the study is ongoing. Newly established POUs with fewer resources participated in this study, and increasing experience with the protocol may result in decreasing toxicity.

The rate of treatment failure is in keeping with studies in well-resourced settings[17] and lower than in a similar setting in Iran,[18] although the latter study did not have histological confirmation, and refractory disease was diagnosed based on end-of-treatment PET-CT. Numerous studies have failed to show survival benefit with end-of-treatment (EOT) PET-CT in lymphoma.[19] The incidence of relapsed disease will require more time on study and the accrual of more patients over time to indicate whether these results will hold.

According to the study protocol, radiotherapy was indicated in 46% of patients, but only 56% of these received this treatment, and there was a significant difference in 2-year OS but not PFS between patients who did and did not receive radiotherapy. The role of radiotherapy in HL continues to be explored, and research efforts are ongoing to better define the small group of patients that require this modality for cure. An 80% OS was achieved in a study of patients in Burkina Faso, Cameroon, Mali, Madagascar and Senegal, low-income countries without access to radiotherapy.[20]

Although seven patients were inappropriately treated on the intermediate-risk rather than the high-risk arm, the OS is still high. As South African clinician-researchers continue to gain experience in protocol-based harmonised treatment and clinical trials, we anticipate that adherence to protocols will improve. This relatively large patient cohort observed prospectively, adds valuable insights into the treatment of children and adolescents with HL, and is generalisable to a middle-income setting as there were no exclusions based on HIV status or prior comorbidities, a common factor in clinical trials.

Although this study protocol encouraged bone marrow biopsy for all patients, it is no longer required in settings that have PET-CT facilities available.[21] Unfortunately, most African countries do not have access to this diagnostic modality and thus should continue to perform bone marrow biopsies, especially in patients with suspected late-stage disease.

This collaborative effort using a risk-stratified and response-adjusted treatment regimen that incorporated agents with a favourable toxicity profile, which are readily available in the local setting and which can be administered on an outpatient basis, resulted in improved survival of children with HL in South Africa.

4.1 | Limitations

Although we enrolled the majority of children with HL in South Africa during the study period, the numbers are small, and robust conclusions are yet to be derived. The proportion of patients with unspecified histological subtypes reflects suboptimal access to paediatric surgery for lymph node excision, as well as a certain number of patients who were too ill at diagnosis to undergo invasive procedures. Overdiagnosis of relapsed or refractory disease should be mitigated by a forthcoming national protocol to diagnose and treat such disease in South Africa. Relapse rates may increase as patients spend more time on the study. Failure to adhere to the protocol and inconsistent access to PET-CT facilities represent challenges in the middle-income setting.

4.2 | Recommendations

Following the success of a harmonised treatment guideline for HL, guidelines for the remaining WHO index cancers should be completed and implemented in South Africa. Multiple studies have now demonstrated the success of ATRs in LMIC, and we thus encourage other countries and cooperative groups to craft ATRs tailored to their individual settings while still following accepted guidelines. In addition, analysing and disseminating results of ATR implementation to accrue sufficient patient numbers for conclusive results are recommended. Children with HIV and HL should receive risk-stratified, response-adapted therapy, with additional supportive care and the option to de-intensify treatment if necessary.

5 | CONCLUSION

In South Africa, risk stratification for HL appears to correlate with prognosis, although larger numbers are required to confirm this with statistical significance. Response-adapted therapy is feasible, although challenging, in South Africa and contributes to a patient-centred approach. The 2-year OS of both HIV-positive and HIV-negative patients has improved dramatically since 2010, most likely due to standardisation of supportive care. This analysis suggests improved OS over time, partially ascribed to standardised treatment and increased supportive care. The improved survival lends strength to the harmonisation movement and gives hope that South Africa will achieve the GICC goals.

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CONFLICT OF INTEREST STATEMENT

The authors declare they have no conflicts of interest.

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DATA AVAILABILITY STATEMENT

The dataset for this study is available on request.

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SUPPORTING INFORMATION

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