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Treatment outcomes of children with Hodgkin lymphoma between 2000 and 2010: First report by the South African Children's Cancer Study Group

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Abstract

Background: Children with Hodgkin lymphoma (HL) have excellent survival rates in high-income countries, but there are minimal outcome data in South African patients. Differing approaches to treatment are used in centres across South Africa, and the South African Children's Cancer Study Group (SACCSG) embarked on a programme to audit outcomes to improve survival rates.

Patients and Methods: A multicentre study was conducted to analyse outcomes and prognostic factors of children with HL in South Africa. Ten dedicated South African paediatric oncology units participated in a retrospective data review. All patients with HL treated consecutively between January 2000 and December 2010 were included. Kaplan–Meier curves and Cox regression model were employed to determine survival rates and prognostic factors.

Abreviations: ABVcD–ChlVbPP, adriamycin, bleomycin, vincristine and dacarbazine–chlorambucil, vinblastine, prednisone and procarbazine; ABVD, adriamycin, bleomycin, vinblastine and dacarbazine; AIHA, autoimmune haemolytic anaemia; ARV, antiretroviral; CI, confidence interval; CT, computed tomography; FDG-PET–CT, fluorodeoxyglucose-positron emission tomography–computed tomography; HIC, high-income country; HIV, human immunodeficiency virus; HL, Hodgkin lymphoma; ITP, immune thrombocytopaenic purpura; LMIC, low- and middle-income country; LMP, latent membrane protein; MRI, magnetic resonance imaging; OPPA/OEPA-COPP, vincristine, procarbazine/etoposide, prednisone and doxorubicin; OS, overall survival; POU, paediatric oncology unit; SACCSG, South African Children's Cancer Study Group

Results: Two hundred and ninety-four patients were eligible for inclusion. The median age at presentation was 9.6 years (range 2.9–18.8); 55.4% of the patients presented with Stage III and IV disease and 9.9% were human immunodeficiency virus (HIV) positive. First-line therapy consisted of adriamycin, bleomycin, vinblastine and dacarbazine (ABVD) in 158 patients, vincristine, procarbazine/etoposide, prednisone and doxorubicin in 97 and adriamycin, bleomycin, vincristine and dacarbazine–chlorambucil, vinblastine, prednisone and procarbazine in 23 patients. The 5-year overall survival (OS) was 79% (95% confidence interval 73–84%). Multivariate analysis demonstrated that HIV infection ($P = 0.018$) and Ann Arbor Stage III and IV disease ($P = 0.006$) conferred a poor prognosis, while treatment with ABVD was associated with higher survival rates ($P = 0.028$).

Conclusion: OS rates are encouraging for a middle-income country, although economic disparities continue to impact negatively on outcomes. Study results will form the basis for the development of national protocol and continued advocacy to rectify disparities.

KEYWORDS

Hodgkin disease, prognostic indicators, SACCSG, South Africa

1 | INTRODUCTION

Survival rates of children with Hodgkin lymphoma (HL) in excess of 90% are well documented in high-income countries (HICs).[1] South Africa is an upper middle income country of 54 million people[2] with a healthcare system based on both state and private funding. Gross inequalities between the public and private healthcare sectors have persisted and in places widened since 1994, with the inception of democracy in South Africa. The public healthcare sector is heavily subsidised from the national fiscus, while the private healthcare sector is funded by the individuals receiving health care and medical insurers. Inequitable access to health care, financial constraints, limited follow-up, co-morbid disease (particularly tuberculosis, human immunodeficiency virus [HIV] and chronic malnutrition) continue to challenge effective healthcare delivery in South Africa.[3] In addition, maladministration has contributed to disparities in healthcare provision across different provinces in the country.[4] The burden of HIV disease grew in the period 1994 to the present and has only recently started to diminish with the widespread availability of state-funded antiretroviral (ARV) medication since 2003.[5,6] HL has established itself as an HIV-related malignancy in the adult HIV-infected population,[7] but a similar trend has not been identified in the paediatric population in African studies.[8–10]

Challenges to childhood cancer treatment in low- and middle-income countries (LMICs) include limited or erratic access to chemotherapy, radiotherapy and specialised services.[11] Various approaches to treatment of HL have been applied, including regimens that include[12] or exclude[13] radiotherapy in equivalent socio-economic settings with satisfactory results. In South Africa, patients have been treated on a variety of hybrid or single-arm protocols with or without radiotherapy, according to institutional preference.

The South African Children's Cancer Study Group (SACCSG) was founded in 1987 to coordinate paediatric cancer care at various sites. Political and economic challenges have resulted in the group assuming an advocacy role for many years, but the focus has recently shifted from one of service delivery to multi-centre cooperation and dissemination of research findings in an effort to improve survival rates. In October 2013, the organisation undertook to report its national HL data from both the public and private health sectors. This article represents the cumulative efforts of all dedicated paediatric oncology units (POUs) in the country to determine survival rates and prognostic factors in a South African population. This report is a retrospective review of all children with HL diagnosed and treated in South Africa between 2000 and 2010.

2 | MATERIALS AND METHODS

2.1 | Patient population

This multi-centre retrospective study included all histologically confirmed, treatment-naive cases of HL in patients 18 years and younger who presented to the 10 dedicated South African POUs from January 1, 2000 to December 31, 2010. Exclusion criteria included patients with records that were markedly incomplete. In the majority of patients, the diagnosis was established by pathologists of the National Health Laboratory Services, ensuring relatively uniform assessment, with review by a single pathologist as required during the course of this review.

2.2 | Staging and imaging

Patients were staged clinically and radiologically according to the Ann Arbor classification system.[14] Investigations included chest x-ray, computed tomography (CT) or magnetic resonance imaging (MRI) of the neck, chest and abdomen, as well as bone marrow aspirate and trephine biopsy. Where available, staging with fluorodeoxyglucose-positron emission tomography–CT (FDG-PET–CT) or gallium scintigraphy was performed. Bulky disease was defined as lymph nodes or

lymph node aggregates greater than 6 cm in the long axis, or mediastinal adenopathy greater than 33% of the thoracic diameter.

In patients who received adriamycin, bleomycin, vincristine and dacarbazine–chlorambucil, vinblastine, prednisone and procarbazine (ABVcD–ChlVbPP) and those with Stage II and III disease were assessed at diagnosis and again at the end of treatment with PET–CT, while patients with Stage IV disease underwent mandatory review after the first four cycles of chemotherapy. Patients with complete response or good partial response stayed on protocol and completed the last two cycles, while those with poor response were changed to second-line chemotherapy. Patients on all other protocols were re-assessed at the end of treatment with available imaging as described above.

2.3 | Treatment

The treatment protocols under study included adriamycin, bleomycin, vinblastine and dacarbazine (ABVD),[15] vincristine, procarbazine/etoposide, prednisone and doxorubicin (OPPA/OEPA-COPP)[16] and ABVcD–ChlVbPP.[17] Patients were staged and then treated as follows: in those who received ABVD, patients with Stage I and II disease received four to six cycles, while patients with Stage III and IV disease received six cycles. In the OEPA/OPPA-COPP protocol, two cycles of OEPA/OPPA were planned for Stage I and IIA disease, two cycles of OEPA/OPPA followed by two cycles of COPP for Stage IIB and IIIA disease and two cycles of OEPA/OPPA followed by four cycles of COPP for Stage IIIB, IV, IIEB and IIIE disease. In the ABVcD–ChlVbPP protocol, patients with Stage I disease received two cycles of ABVD and two cycles of ChlVbPP. Patients with Stage II, III and IV disease all received three cycles of ABVD alternating with three cycles of ChlVbPP.

Patients were not treated on prospective trials. Regimens were selected according to institutional preference.

Radiation was included in the ABVD and ABVcD–ChlVbPP protocols for patients with initial bulky disease or those shown to have poor response to first-line chemotherapy (on follow-up CT or PET scanning). Patients who received OPPA/OEPA-COPP were treated as a matter of course with involved field radiation at the end of chemotherapy. Radiation doses ranged from 14 to 44 Gy, with a median of 25 Gy. In units with the capacity to do so, response evaluation was performed at the end of two to three cycles of chemotherapy, although PET–CT scanning was not available in South Africa until the latter part of the study period.

2.4 | Statistical analysis

Data were entered into a central, anonymised database managed by a single researcher. Descriptive statistics were presented. For categorical variables such as sex, ethnic group and HIV status, frequency tables were presented. For continuous variables such as age, summary measures were presented using mean with standard deviation if data were normally distributed, otherwise the median with range was reported. Other variables included histological subtype, stage, treatment regimen, treatment site, toxicity rates and causes of death. Potential differences between independent groups were elucidated using Student *t*-test or Mann–Whitney U test. Overall descriptive survival was evaluated using Kaplan–Meier analysis. Overall survival (OS) was defined from the date of diagnosis until the date of death or date last seen. Event-free survival was calculated from date of diagnosis until disease progression or death. Treatment failure was calculated from the date of diagnosis until the date of progression of disease, relapse or death from any cause. Refractory disease was diagnosed in those patients who failed to obtain a complete response with initial therapy or those who relapsed within 3 months from the end of initial therapy. Late relapse was defined as relapse more than 6 months from the completion of therapy. Treatment abandonment was defined as failure to initiate or complete treatment with a curative intent, except when the treating physician elected to stop treatment. 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. These patients were censored in the survival curves. To assess the statistical significance of various prognostic factors, univariate and multiple Cox regression modelling technique was used with death defined as an end point. All factors found significant at 20% level in the univariate level were considered for adjustment in the multiple regression models. For all other calculations, a P value of less than 0.05 was considered significant. Permission to conduct retrospective analyses was obtained from the relevant human research ethics committees at individual study sites. The cut-off for data analysis was October 2015.

3 | RESULTS

In total, 301 cases of HL were reported from January 2000 to December 2010, representing 3.7% of the total number of reported malignancies in South African children during this interval.[18] The reported age-standardised ratio during this period was 2.2 per million.[18] The demographic data and disease characteristics on presentation are shown in Table 1. Data from six patients were excluded, as they were treated elsewhere, and one patient was found not to have HL at review of histology. The incidence of HL increased with age and a male predominance (sex ratio of 3.3:1) was shown. The majority of the patients were of African ancestry (217), followed by 43 of mixed ancestry, 22 of Caucasian and 12 of Indian descent. The median age was 9.6 years (range 2.9–18.8 years). with no significant difference in ages linked to ethnicity. The majority of patients (63.6%) were younger than 11 years of age, although it must be noted that individual institutional policies dictated that certain units treat patients up to the age of 12 years, some to 15 years and some to 18 years. Male patients were significantly younger than female patients, with a median of 9.3 years versus 11 years in females ($P = 0.0158$). Twenty-nine (9.9%) of the patients were HIV positive (Table 1). Only 9 of the 29 HIV-positive patients were on ARV therapy at the time of diagnosis of HL, and 7 of these had undetectable HIV viral loads. Data on the duration of ARV treatment prior to presentation were not included in this study. The national roll-out of state-funded ARV therapy started in November 2003[6] and thus

TABLE 1 Characteristics of 294 South African children with HL at presentation

Characteristic	N = 294 (%)
Age	
0–5 years	51 (17.3)
6–10 years	136 (46.1)
>10 years	107 (36.6)
Sex	
Male	225 (76.6)
Female	69 (23.4)
HIV status	
Negative	265 (90.1%)
Positive	29 (9.9%)
Ann Arbor Stage	
I	22 (7.5)
II	108 (37.1)
III	83 (28.2)
IV	80 (27.2)
Undocumented	1 (0.3)
Histological subtype	
Classical HL	
Nodular sclerosing	125 (42.5)
Mixed cellularity	120 (40.8)
Lymphocyte depleted	12 (4.1)
Lymphocyte rich	0 (0)
Nodular lymphocyte predominant	9 (3.1)
Interfollicular	2 (0.7)
Unclassified	26 (8.8)
Systemic B symptoms	
Yes	174 (59.2)
No	117 (39.8)
Undocumented	3 (1)
Bulky disease	
Yes	114 (38.8)
No	179 (60.9)
Undocumented	1 (0.3)

many patients were not afforded access to ARV therapy in the earlier part of the study period.

The majority of patients presented with Stage III and IV disease (55.4%) and B symptoms (59.2%). Children with HIV presented with more late stage disease (23/29, 79%) than their HIV-negative counterparts (135/254 53%, $P = 0.002$). There was no correlation between ethnicity and late presentation (Student *t*-test, $P = 0.45$, correlation coefficient 0.0443). Patients with Stage IV disease (n = 80) included 25 with bone marrow involvement, 6 with bone involvement, 3 with liver involvement, 32 with a combination of bone, bone marrow and liver and 14 with other sites including parenchymal lung disease. Twenty-seven patients (9.5%) presented with autoimmune manifestations which included immune thrombocytopaenic purpura (ITP) in 4 patients, nephrotic syndrome in 4 and autoimmune haemolytic anaemia (AIHA) in 10 patients, the combination of AIHA and ITP in 5 patients and rheumatoid arthritis in 4 patients. In addition, one patient presented with secondary haemophagocytic lymphohistiocytosis. Bulky disease was present in 38.8% of the patients. Histological subtypes are represented in Table 1. Only 153/294 (52%) specimens were tested for Epstein–Barr virus latent membrane protein (LMP) expression and 22 (14.4%) of these demonstrated LMP expression.

At presentation, there were no statistically significant differences between patients of different ethnic groups with respect to median age, HIV status, history of B symptoms, bulky disease and histological subtypes. However, autoimmune manifestations of HL were more common in patients of African ethnicity ($P = 0.0177$, Student *t*-test). Of the 29 patients with HIV disease, only 2 presented before the national rollout of combination ARV therapy.

3.1 | Imaging

Radiological investigations on presentation to the treating unit included chest x-ray in 235 patients (79.9%), ultrasound in 97 (33%), CT scan in 269 (91.5%), MRI in 12 (4.1%) and PET–CT in 63 (21.4%). While FDG-PET–CT became standard of care imaging in well-resourced centres worldwide in the period of this study, many South African POUs did not have access to this facility, and in some this only became available near the end of the study period.

3.2 | Management protocols

Eight patients did not receive chemotherapy: one patient had localised disease with nodular lymphocyte predominant subtype which was fully resected and was thus deemed not to require further treatment, while seven patients died of disease before chemotherapy could be started. Of the 286 remaining patients, 158 (55.2%) received ABVD, 97 (33.9%) were given OPPA/OEPA-COPP, 31 (10.8%) received ABVcD–ChlVbPP hybrid protocol and 8 (2.9%) received other combinations (Supplementary Fig. S1). Student *t*-test showed no differences between the distributions of patients on the different treatment protocols. Seventeen (5.8%) patients were found to have primary refractory disease and were changed to second-line chemotherapy protocols, although many units did not perform early assessments to determine initial response to therapy. Eighty-three patients received radiation as part of the first-line therapy. Of these, 66 were on the OPPA/OEPA-COPP protocol which incorporated radiation for all patients, while radiotherapy was reserved for bulky or relapsed disease.

3.3 | Haemopoeitic stem cell transplants

Six patients underwent autologous stem cell transplants for relapsed disease: two patients demised from progressive disease, three achieved long-term survival and one was alive with disease at close of the study date.

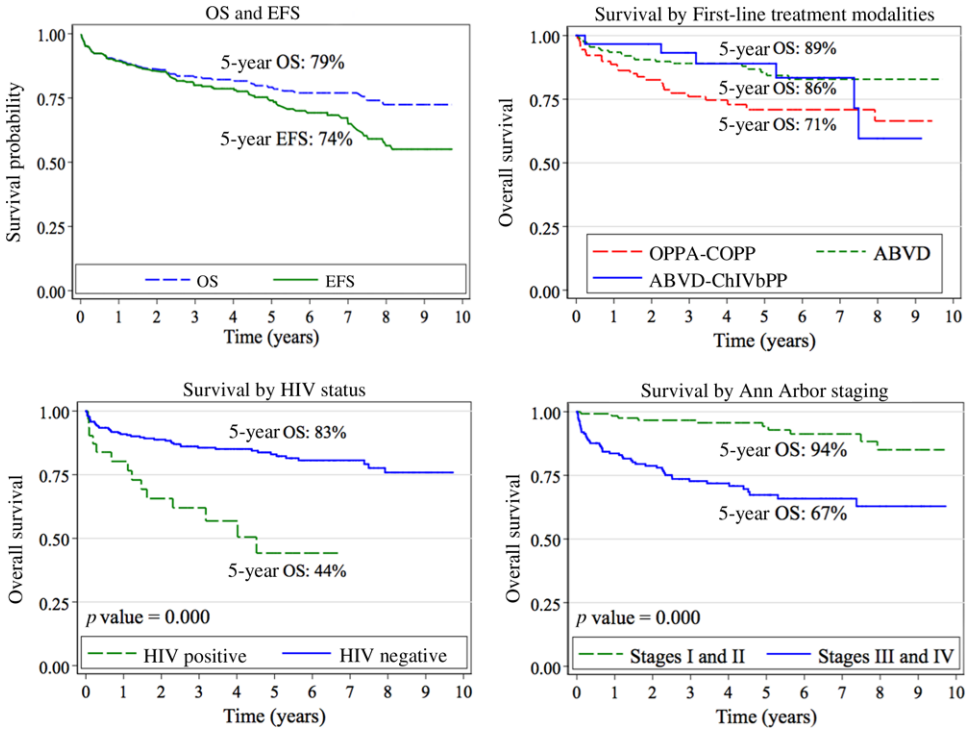

FIGURE 1 Kaplan–Meier survival curves of patients treated for HL in South Africa

3.4 | Overall survival

The 5-year OS rate by Kaplan–Meier analysis for the entire cohort was 79% (95% confidence interval [CI] 73–84%), with a median survival of 4.1 years (interquartile range 1.92–6.46). The 5-year OS for Stage I was 100%, Stage II was 93.2% (95% CI 85.2–96.9%), Stage III was 77.4% (95% CI 65.5–85.7%) and Stage IV was 56.2% (95% CI 42.5–67.9%) (see Fig. 1).

There was a marked discrepancy in survival rates between different units, ranging from 20% in a newer, less well-resourced unit to 95.5% in a well-established, adequately resourced POU in a province with a fully functioning healthcare system. The two newer units treated patients who presented with Stage IV disease in five out of six cases and Stage III disease in four out of five cases, respectively. Forty patients demised from their disease, 13 died from infections (bacterial, viral and tuberculous), 1 had a severe dilated cardiomyopathy and 1 died of an unknown cause. Two patients developed second malignant neoplasms: one patient developed osteosarcoma and demised 5 years from the original HL diagnosis and a second patient developed a primitive neuroectodermal tumour of the brain and demised 4.5 years from the diagnosis. Patients with documented primary refractory disease constituted 8.5% of the total number of patients who received chemotherapy (Supplementary Table S1), 13 (4.5%) relapsed in 6 months from the completion of therapy, while 23 (8%) relapsed more than 6 months after the completion of therapy.

3.5 | Poor prognostic factors

These results demonstrated that children older than 10 years (75.9 vs. 82.2%) with HIV infection (44.2 vs. 83.0%) and Stage III and IV disease (77.4 and 56.2%, respectively) had lower survival rates. This is in line with univariate analysis which demonstrated statistically significant differences in survival rates associated with age ($P < 0.05$), HIV infection ($P < 0.001$), B symptoms ($P = 0.001$), stage of disease ($P = 0.006$) and ethnicity ($P = 0.001$) (see Table 2). Patients of African descent had the lowest survival rate of 72.9% compared to over 90% in other ethnic groups ($P = 0.001$), but multivariate analysis did not confirm ethnicity as an independent prognosticator.

A difference in survival rates was shown to be associated with the chemotherapy regimen used ($P = 0.028$): children treated with ABVD had higher survival rates (85.6%) than those treated with OEPA/OPPA-COPP (70.9%) and ABVcD–ChlVbPP (82.3%). The influence of sex and the presence of bulky disease did not exert a statistically significant effect on survival. In Supplementary Table S1, it appears that there were more cases of treatment-related mortality using the OEPA/OPPA-COPP regimen (ABVD 5/158 = 3.2%, ABVcD–ChlVbPP 0/31 = 0% and OEPA/OPPA-COPP 11/97 = 11.3%), but the differences between the groups were not statistically significant. The small sample size does not allow for more in-depth discussion and analysis.

After adjusting for all significant factors, the multiple regression analysis showed that prognostic factors significantly associated with lower survival rates were HIV infection ($P = 0.018$), Ann Arbor Stage III and IV disease ($P = 0.006$) and treatment with chemotherapy protocols other than ABVD ($P = 0.028$) (Table 3).

3.6 | Follow-up

The rate of early treatment abandonment was 4.9%. The median follow-up period was 4.4 years, with a range of 0–13.8 years. The rate

TABLE 2 Univariate risk factor analysis of presenting features of patients with HL and chemotherapy regimens

Variables	5 year OS (%)	Hazard ratio	95% CI, lower	95% CI, upper	*P* value, Cox regression
Sex					
Male	82.2	Ref			
Female	70.6	1.60	0.93	2.74	0.089
Age					
<10 years	82.2	Ref			
>10 years	75.9	1.56	0.93	2.61	0.094
Ethnicity					
African	72.9	Ref			
Mixed	94.6	0.22	0.07	0.72	0.012
Indian	100	0.28	0.04	2.05	0.211
Caucasian	95.2	0.15	0.02	1.09	0.061
Histologic subtype					
Classical HL					
Nodular sclerosing	80.1	Ref			
Mixed cellularity	85.2	0.73	0.40	1.34	0.311
Lymphocyte depleted	71.6	1.42	0.43	4.73	0.563
Nodular lymphocyte predominant	66.7	0.76	0.10	5.59	0.785
B symptoms					
Present	72.9				
Absent	88.8	0.33	0.18	0.63	0.001
HIV infection					
Yes	44.2	Ref			
No	83.0	0.28	0.15	0.52	<0.001
Ann Arbor Stage					
Stage I[a]	100				
Stage II	93.2	Ref			
Stage III	77.4	2.57	1.17	5.61	0.018
Stage IV	56.2	5.84	2.85	11.99	<0.001
Chemotherapy					
OEPA/OPPA-COPP	70.9	Ref			
ABVD	85.6	0.47	0.26	0.85	0.012
ABVD–ChlVbPP/other	82.3	0.84	0.39	1.82	0.667

[a]No deaths recorded.
Ref denotes the reference value against which other values were compared.

of loss-to-follow-up was also 4.9%. Of the 12 patients who were lost to follow-up once they had completed their scheduled therapy, 8 were lost to follow-up before 2 years and 4 were lost to follow-up after 2 years.

4 | DISCUSSION

This study marks a landmark in the history of the SACCSG, as it is the first report of South African oncology patients in which all POUs contributed data. More than half the patients in this study presented with Stage III and IV disease, in keeping with reports from other LMICs.[19–22] The OS rate compares favourably with that in other upper middle income countries, but there are numerous opportunities for improvement.

Published reports of lower survival rates in patients of African ancestry, as well as the finding on univariate analysis of a poorer survival outcome in patients of African descent, prompted a closer examination of these patients. Similar findings have been postulated to be associated with a higher incidence of mixed cellularity and lymphocyte predominant subtypes,[20,21] as occurs in suboptimal socio-economic conditions, but this was not confirmed in this study. While there was no demonstrable difference in distribution of patients according to histological subtype, presence of B symptoms or bulky disease, age at presentation or HIV status, there appeared to be a preponderance of late stage disease in African patients, but this was not statistically

TABLE 3 Results of the adjusted Cox regression model for factors associated with survival among patients with HL

Variables	Hazard ratio	95% CI, lower	95% CI, upper	*P* value, Cox regression
Sex				
Male	Ref			
Female	1.71	0.94	3.13	0.081
Age				
<10 years	Ref			
>10 years	1.53	0.83	2.80	0.172
Ethnicity				
African	Ref			
Mixed	0.30	0.09	1.01	0.052
Indian	0.35	0.05	2.63	0.310
Caucasian	0.15	0.02	1.09	0.060
HIV infection				
Yes	Ref			
No	0.46	0.22	0.99	0.047
Ann Arbor Stage				
Stage I[a]	-			
Stage II	Ref			
Stage III	2.31	1.01	5.28	0.048
Stage IV	3.22	1.43	7.25	0.005
Chemotherapy				
OEPA/OPPA-COPP	Ref			
ABVD	0.45	0.24	0.83	0.011
ABVD-ChlVbPP/other	1.30	0.57	3.00	0.532

[a]No deaths recorded.
Ref denotes the reference value against which other values were compared.

significant. Multivariate analysis did not confirm African ancestry as an independent risk factor for poor prognosis, suggesting that other factors such as lack of access to quality care and delayed diagnosis may play a role. Although this study did not confirm an increase in late presentation in patients of African ethnic background, it is likely that many of these patients were not diagnosed or referred to specialist centres, as it has been clearly documented that African patients in South Africa are under-represented in the published incidence rates and age-standardised ratios.[18]

A major limitation of many biomedical studies that report on survival rates in relation to race and ethnicity is the failure to define what is meant by the particular classification used.[23] In the South African context, it is impossible to deny or ignore racial or ethnic health disparities, no matter how individuals are classified. While "race" has been employed as a surrogate marker for socio-economic conditions in various studies,[21,24] this postulate has not been validated and thus remains a question to be interrogated prospectively.

The Type 1 epidemiological pattern, comprising mainly mixed cellularity and lymphocyte-depleted subtypes, is said to be characteristic of low-income countries. The Type 3 pattern, noted in HICs, is characterised by mainly nodular sclerosing subtype and less marked male predominance.[25] South African children with HL appear to fall into a Type 2 pattern, as found in a "developing" country[26,27] based on the marked male predominance, equal proportions of mixed cellularity and nodular sclerosing subtypes and majority presentation in the first decade of life. It is possible that varying upper age limits for admission to South African POUs may have skewed the data towards the younger age groups. Previous reports have demonstrated the striking relationship between socio-economic and environmental factors and affected age groups,[25,26,28] stating that an increased proportion of younger children with HL is found in countries with poor socio-economic conditions.

The HIV incidence rate of 9.9% in this cohort parallels the rate of HIV infection in the country during this period,[2] reflecting the findings of three South African studies[8,10,29] and a Malawian study[9] which did not confirm an increased incidence of HL in an HIV-positive paediatric population. ARV therapy became available to affected children in 2003[6] and thus the outcome of some of these patients may have been affected by the lack of access to definitive treatment.

The incidence of autoimmune disease at diagnosis of HL is comparable to rates reported in a limited number of studies, which range between 2.6 and 13.6%.[30–32]

The low rate of treatment abandonment, lower than in many other LMICs,[33,34] reflects the tenacity of the clinical teams and the assistance of non-profit organisations in augmenting psycho-social services.

The 5-year OS rate of 79% is encouraging for a middle-income country with a fragmented healthcare system. The refinement of imaging and supportive treatment modalities over time has undoubtedly contributed to lower relapse rates in this group of patients. The priority for South African paediatric haemato-oncologists is to improve survival rates while limiting toxicities. Not all South African POUs are well equipped to deal with severe treatment-related toxicities: as an example, most hospitals have very limited intensive care facilities[35] which often cannot accommodate patients with malignancy-related complications. With stem cell transplant only available in three state-funded institutions, and newer agents as yet unregistered for use in South Africa, access to more sophisticated salvage therapy options is limited. Issues such as chemotherapy-induced infertility are generally not considered priorities by health regulators in middle-income countries such as South Africa and it thus behoves clinicians to highlight these issues in long-term healthcare planning for children with cancer. The findings of this study may be of benefit for clinicians in other LMICs, where the majority of children with cancer are treated.

5 | CONCLUSIONS AND RECOMMENDATIONS

The choice of treatment regimen is partially determined by the cost and availability of individual chemotherapeutic agents and radiation in particular institutions. The group of patients described here had a satisfactory survival rate, but certain subgroups require increased attention to improve OS: these include patients with HIV infection and those who present with late stage disease. This OS, while seemingly satisfactory for a middle-income country, has the potential to improve within the existing infrastructure, and thus mandates the harmonisation of treatment regimens in order to provide a uniformly good level of service across all units. A prospective study incorporating risk-adapted therapy has been designed on the basis of the results of this study and will aim to improve survival rates and limit late effects while using the most accessible and widely used modalities.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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Additional Supporting Information may be found online in the supporting information tab for this article.

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