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ORIGINAL ARTICLE

Hodgkin lymphoma at Groote Schuur Hospital, South Africa: the effect of HIV and bone marrow infiltration

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Abstract

Human immunodeficiency virus (HIV) is associated with an increased risk of developing Hodgkin lymphoma (HL). South Africa (SA) has the highest HIV prevalence rate in the world. There is currently no outcome-based data for HIV-associated HL from SA. A bone marrow database was compiled of all bone marrow biopsies (BMB) reported at National Health Laboratory Service (NHLS) Groote Schuur Hospital (GSH) between January 2005 and December 2012. Patients who had a BMB performed for staging of HL or where HL was diagnosed on the BMB were included for further analysis. Clinical and laboratory data was extracted from medical and laboratory records. Primary outcome measures included histological subtype, bone marrow infiltration (BMI) by HL, CD4 count, HIV-viral load (HIV-VL), tuberculosis (TB) data, treatment with chemotherapy and 5-year overall survival (OS). The database included 6569 BMB and 219 patients of these had HL and were included for analysis. The median age at presentation (32 years) was similar in the HIV+ and HIV− populations. While males predominated in the HIV− group, females predominated in the HIV+ group (male:female ratio of 1.5:1 vs 0.7:1, respectively). The majority of patients (71%) were HIV negative (HIV−) and 29% were HIV positive (HIV+). The diagnosis of HL was made on BMB in 17% of cases. BMI was seen in 37% (82/219) overall, and was found in more HIV+ patients (61%; 39/64) than HIV− patients (28%; 43/155; $p = 0.03$). The histological subtype varied according to HIV status with nodular sclerosis classical Hodgkin lymphoma (NSCHL) being most frequent in the HIV− group and classical Hodgkin lymphoma (CHL)-unclassifiable the most frequent in the HIV+ group. HIV+ patients had a median CD4 count of 149×10^6/L and 39% were anti-retroviral therapy (cART) naive at HL diagnosis. HIV+ patients had received anti-TB therapy more frequently than HIV− patients (72% vs 17%; $p = 0.007$). More HIV+ patients did not receive chemotherapy than HIV− patients (31% vs 3%; $p = 0.001$). The 5-year OS was 56%. HIV+ patients with BMI had a 5-year OS of 18%. BMI, HIV status, low CD4 count, histological subtype and TB therapy had a statistical significant impact on 5-year OS ($p < 0.01$). The 5-year OS was 56%, with both BMI and HIV+ status being associated with poor survival. BMB provided the diagnosis of HL in 17% of cases, confirming its diagnostic utility in our setting. Our cohort showed similar survival outcomes to other countries in Africa, Asia and Central America with comparable socio-economic constraints to SA.

Keywords Hodgkin lymphoma · HIV · Bone marrow · Haematology · Oncology

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Introduction

Human immunodeficiency virus (HIV) infection is associated with an approximately 10-fold increased risk of developing Hodgkin lymphoma (HL) [1, 2]. South Africa (SA) has the highest prevalence of HIV in the world with 12,7% of the South African population infected in 2016 [3, 4], amounting to approximately 7 million HIV infected individuals [4]. HIV-related deaths in SA reached a peak in 2006; however, in the past 10-years, there has been a significant decline from 48% of all deaths in 2006 to 27% of all deaths in 2016 [4]. This improvement has followed the introduction of the antiretroviral therapy (cART) roll-out program which commenced in SA

in 2004 [4]. An estimated 3.4 million people in SA are currently receiving cART, which is the largest HIV treatment program in the world [3]. Most data on HIV-associated HL is from first world settings with a paucity of data from sub-Saharan Africa [5–8]. This investigation reviews the clinical presentation and outcomes of patients with HL that were referred to Groote Schuur Hospital, a regional state facility in the Western Cape, SA.

Histologically, HL is divided into two main categories: classical Hodgkin lymphoma (CHL) and nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) [9]. Based on the histologic features seen on the lymph node, CHL can then be further subdivided into four histological subtypes. The four histological subtypes of CHL include lymphocyte rich CHL (LRCHL), nodular sclerosis CHL (NSCHL), mixed cellularity CHL (MCCHL) and lymphocyte depleted CHL (LDCHL) [9]. HIV-associated HL has been shown to have a different incidence of histological subtypes [10], and the various histological subtypes have differing clinical presentations and clinical outcomes [10, 11].

HL patients with bone marrow infiltration (BMI) are classified with stage IV disease according to the Cotswold revision of the Ann Arbor staging classification [12–15], and BMI is one of the prognostic factors used in the International Prognostic Score (IPS) [16]. Various publications estimate that on presentation approximately 5% of patients with non-HIV HL have BMI [17–19], while in HIV-associated HL, 40% to 50% showed BMI [20–24].

^{18}Fluorodeoxyglucose positron emission tomography (^{18}FDG-PET) fused with CT-scan, also known as a PET-CT, is widely used for staging HL patients in well-resourced settings; however, PET-CT is not widely available on the African continent [25]. In resource-poor settings, including the state health sector of SA, bone marrow biopsies (BMB) play an important role in the staging of HL patients and it is widely practiced that all newly diagnosed patients with HL receive a staging BMB. In addition, where PET-CT is available, the interpretation in HIV-infected patients may be problematic due to inflammation and co-infection [26–28].

In Africa, co-morbidity with opportunistic infections is common [29]. TB is a contagious disease, caused by the bacillus Mycobacterium tuberculosis, and TB can affect any tissue or organ. SA has the third highest incidence of TB in the world [30], with an estimated 73% of TB patients being co-infected with HIV [30]. Granulomatous inflammation of the bone marrow due to TB is a common finding in HIV sero-positive patients presenting with peripheral cytopenias and/or fever of unknown origin [31]. The overlapping signs and symptoms of TB and HL are significant contributors to delayed diagnosis in Hodgkin patients. Due to the high prevalence of TB in HIV sero-positive patients, empiric TB therapy is often used and a diagnostic tissue biopsy is only performed after TB therapy fails. In our setting, this leads to significant delays in the diagnosis of the malignancy.

The HIV pandemic has led to a marked increase in the number of HL cases diagnosed in SA [32–35]. There is currently no 5-year overall survival (OS) outcome-based data available for HIV-associated HL from SA; we undertook this retrospective analysis to evaluate the pathological findings, survival and predictors of survival of HL patients in our setting.

Methods

A retrospective analysis was conducted of adult patients with HL who had a BMB reported at our tertiary referral institution over an 8-year period. The biopsy results were obtained from a bone marrow biopsy registry (BMR) which was compiled for this study. The study sample consisted of every patient entered into the local BMR from 1st of January 2005 to the 31st of December 2012. A CONSORT flow diagram (Fig. 1) reveals the flow of participants through each stage of the study [36]. All follow-up BMB were excluded. Patients who died prior to their staging BMB would have been missed.

Clinical and laboratory data of these patients were extracted from medical and laboratory records. Information collected included age, gender, histological subtype on lymph node, BMI by HL (pos/neg), HIV status, available CD4 counts, HIV-viral load (HIV-VL) data, previous cART exposure, chemotherapy given, viral suppression at diagnosis (defined as HIV-VL of less than 40 copies/ml) and virological failure (using poor CD4 recovery during the course of therapy as a surrogate marker for virological failure), total white cell count (WCC), haemoglobin (Hb), platelet count, lactate dehydrogenase (LDH), erythrocyte sedimentation rate (ESR) and albumin. In addition, clinical information was collected on TB therapy (in the year prior to HL diagnosis) and whether there was laboratory proven TB (organism shown to be present microbiologically and/or histologically).

Outcome variables included 5-year overall survival (OS). Dead or alive status was cross-checked at the Government Department of Home Affairs of SA. The Human Research Ethics Committee (HREC) at University of Cape Town (UCT) approved this study and the creation of the BMR.

Statistical analysis

Outcome variables were compared to predictor variables and the potential confounding variables. A p value of < 0.05 was considered statistically significant. Nominal (categorized) variables were analysed using Fisher's exact

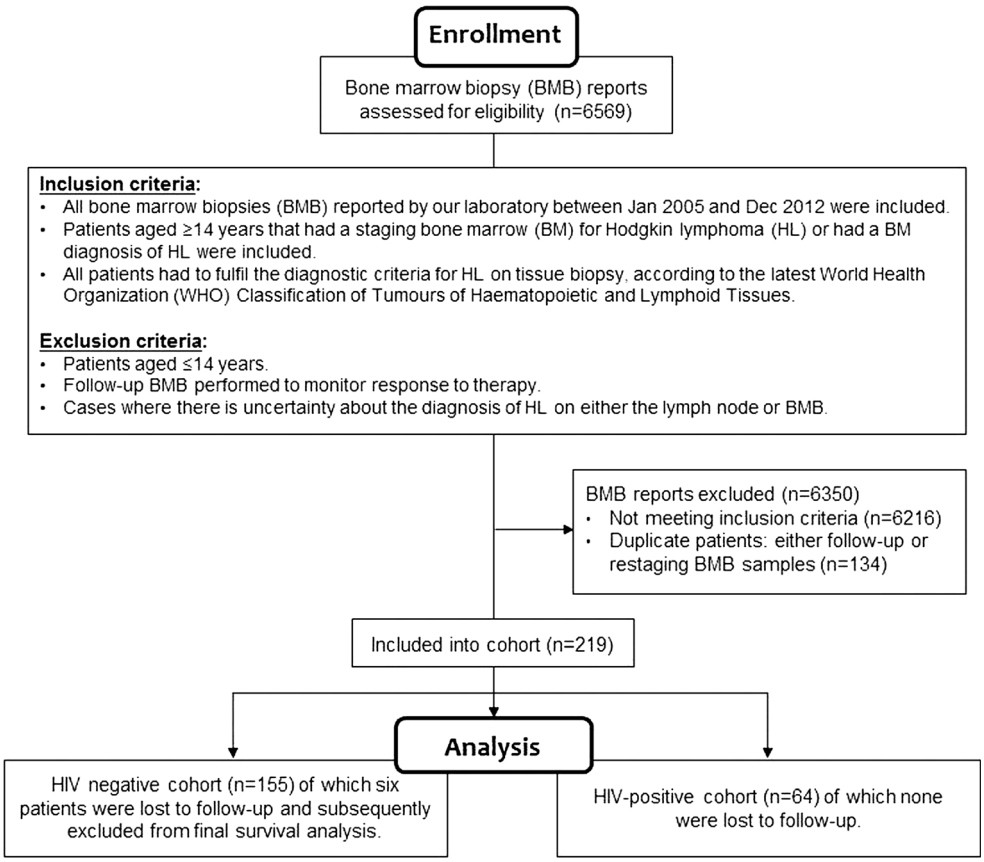

Fig. 1 CONSORT flow diagram

tests and the data presented as proportions. Continuous variables were analysed using Kruskal-Wallis tests and the data presented as medians (interquartile range). Cox proportional hazard regression analysis incorporating Wald's test as well as the likelihood ratio test, were used to estimate the relationship among variables and OS. Odds ratios, adjusted for known variables, were calculated in order to identify which variables carry an increased risk of non-treatment. Survival according to BMI, HL histological subtype, HIV status and different combinations thereof were estimated with the aid of Kaplan-Meier survival curve analysis. Significance in the difference of the survival curves was calculated by the log rank statistic.

Results

Study population

There were 219 HL patients included in this study. The 5-year OS was 56%. Table 1 summarizes the clinical characteristics and laboratory parameters of the study population at the time of diagnosis. While males predominated in the HIV− group, females predominated in the HIV+ group ($p = 0.025$; Fisher's exact test). The median age (32 years) was similar in the HIV+ and HIV− populations, without evidence of the classical bimodal age distribution. One patient previously known with chronic lymphocytic leukemia (CLL) had subsequently developed HL. One patient developed post-transplant HL, 6 years after receiving a haematopoietic stem cell transplant (HSCT) for Burkitt lymphoma. Two years after the diagnosis of CHL, one patient developed treatment-related acute promyelocytic leukemia (tAPL). In addition, two patients developed diffuse large B-cell lymphoma (DLBCL) 1 year after the initial HL diagnosis.

HIV status and marrow infiltration

Of the 219 patients included, 71% (155/219) were HIV− and 29%(64/219) HIV+. BMI was seen in 37% (82/219), and BMI was seen more commonly in HIV+ patients (61%; 39/64) than in HIV− patients (28%; 43/155; Fisher's exact test: $p = 0.03$). Concurrent HIV+ and BMI showed a significantly adverse effect on 5-year OS (Log-rank test; $p < 0.0001$); shown in Fig. 2. HIV+ patients with BMI had a 5-year OS of 18% with 51% (20/39) dying within 3 months of diagnosis. HIV− patients with BMI also showed poor outcomes with a 5-year OS of 48%. However the 5-year OS in HIV+ patients without BMI (5-year OS of 80%) was better than in their HIV− counterparts (5-year OS of 67%).

Table 1 The clinical characteristics and laboratory parameters at the time of diagnosis. The statistical impacts on 5-year OS are as follows: *significant at $p < 0.05$; **significant at $p < 0.005$; ***significant at $p < 0.001$; $^{\Delta}$not significant at $p > 0.05$

Clinical Characteristics	HIV-positive: n=64(29%)	HIV-negative: n = 155(71%)	Entire Cohort: (n=219)
Age (years); median(range)$^{\Delta}$	33(21-51)	32(14-83)	32(14-83)
Gender (M/F)$^{\Delta}$	28/36	94/61	122/97
Bone marrow infiltration; n(%)***	39(61%)	43(28%)	82(37%)
Received chemotherapy***	44(69%)	150(97%)	194(89%)
Combination antiretroviral therapy (cART); n(%)$^{\Delta}$			
• No cART prior to diagnosis.	25(39%)		
• Commenced cART less than 3 months prior to diagnosis.	9(14%)		
• Commenced cART greater than 3 months prior to diagnosis.	30(47%)		
Mycobacterium tuberculosis (TB); n(%)			
• TB work-up done	55(86%)	75(48%)	130(59%)
• Received TB therapy***	46(72%)	26(17%)	72(33%)
• Laboratory proven TB$^{\Delta}$	12(19%)	9(6%)	21(10%)
Hodgkin lymphoma subtype; n(%)***			
• NSCHL	17(27%)	96(62%)	113(52%)
• MCCHL	13(20%)	16(10%)	29(13%)
• LRCHL		2(2%)	2(1%)
• LDCHL		3(2%)	3(1%)
• CHL-unspecified	34(53%)	25(16%)	59(27%)
• NLPHL		13(8%)	13(6%)
Survival and Death; n(%)			
• Died within 1 month of diagnosis	18(28%)	8(5%)	26(12%)
• Died between months 1 to 3	9(14%)	5(3%)	14(6%)
• Died between months 3 to 12	4(6%)	12(8%)	16(7%)
• Died after 1 year	6(10%)	40(26%)	46(21%)
• Still alive	27(42%)	84(54%)	111(51%)
• Unknown (lost to follow-up)		6(4%)	6(3%)

Laboratory parameters	HIV-positive:	HIV-negative:	Entire Cohort:
Leucocyte count (x10^9/L); median(range)$^{\Delta}$	4.04(0.33-22.25)	9.96(1.25-75.98)	7.74(0.33-75.98)
Haemoglobin (g/dL); median(range)***	7.8(2.8-15.1)	11.2(3.9-17.3)	10.3(2.8-17.3)
Platelets (x10^9/L); median(range)***	224(5-675)	408(6-1214)	339(5-1214)
LDH (U/L); median(range)**	573(175-1592)	523(150-3634)	538(150-3634)
ESR (mm/hr); median(range)*	75(0-150)	51(1-150)	56(0-150)
Albumin (g/L); median(range)***	28(12-54)	37(16-54)	34(12-55)
CD4-count (x10^6/L); median(range)**	149(6-1074)		

Influence of immune suppression in HIV positive HL patients

At diagnosis, the HIV+ cohort had a median CD4 count of 149×10^6/L. The CD4 count had a statistically significant impact on 5-year OS (Kruskal-Wallis test: $p = 0.0009$; Fig. 3). Sixty one percent (39/64) of HIV+ patients did not have HIV-VL data. Viral suppression at diagnosis and virological failure failed to show a statistical significant effect on 5-year OS (Fisher's exact test: $p > 0.1$).

Tuberculosis

Thirty three percent (72/219) HL patients received anti-tuberculosis therapy during the year prior to HL diagnosis, comprising 72% (46/64) of the HIV+ cohort and 17% of the HIV− cohort (26/155; Fisher's exact test: $p =$

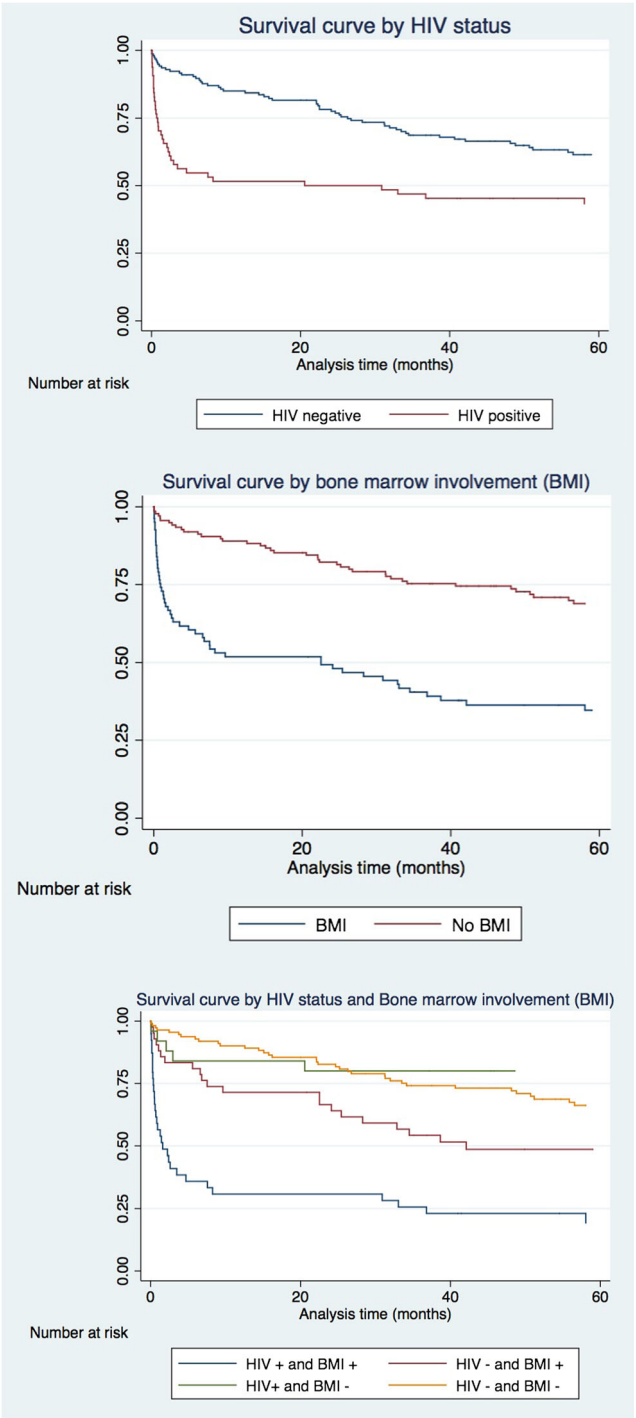

Fig. 2 Impact of HIV and bone marrow involvement on survival in Hodgkin lymphoma

0.0005). Of all HL patients 10% (21/219) had laboratory proven tuberculosis; the majority were HIV+. Two patients had Gibbus deformity due to vertebral collapse caused by advanced skeletal tuberculosis. One had multi-drug resistant tuberculosis (MDR-TB). The 5-year OS of those who received TB therapy was significantly worse (Fisher's exact test: $p = 0.0005$) than those who did

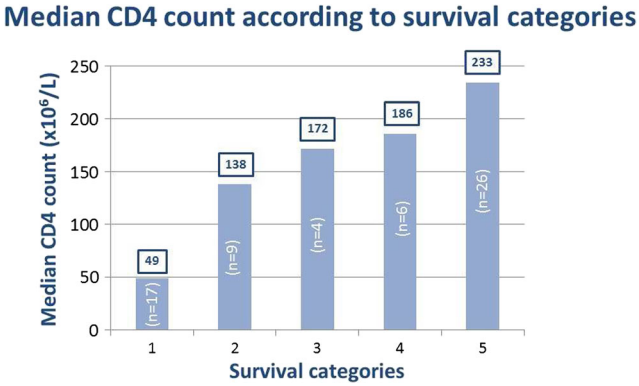

Fig. 3 Relationship between CD4 count and survival in patients with Hodgkin lymphoma: 1 = died within 1 month; 2 = died between 1 and 3 months; 3 = died between 3 and 12 months; 4 = died after 1 year; 5 = alive at the time of analysis

not; however, the presence of a laboratory proven organism did not affect outcome (Fisher's exact test: $p = 0.41$).

Histological subtype

The HL subtype varied according to HIV-status (Table 1) with NSCHL being the most common subtype in HIV- and CHL-unclassifiable, the most common subtype in the HIV+ group. Clinical outcomes varied amongst the different HL subtypes (Fig. 4), which had a statistically significant impact on 5-year OS (Log-rank test; $p < 0.0001$). The diagnosis of HL was made on BMB in 17% (37/219) of patients without the aid of a lymph node biopsy (LNB) and 49% (18/37) of these died within a month of diagnosis, with a median 5-year OS of 25% in the HIV− group and 5% in the HIV+ group. The typical indications for performing a BMB were significant cytopenias and/or fever of unknown origin. Where the diagnosis of CHL was made on BMB, no LNB was obtained and further histological classification was not possible and these cases were added to the CHL-unclassifiable subtype.

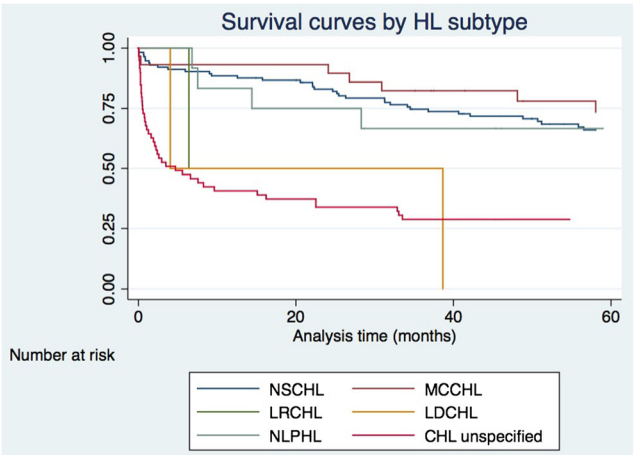

Fig. 4 Impact of histological subtype on survival in Hodgkin lymphoma

Chemotherapy

Overall 89% (194/219) of all HL patients received chemotherapy; 69% (44/64) of the HIV+ and 97% (150/155; Wald test: $p < 0.0001$) of the HIV− cohort. Of the 25 patients that did not receive chemotherapy, 92% (23/25) had BMI and 80% (20/25) were HIV+. In the HIV+ cohort, 31%(20/64) did not receive chemotherapy, of which 14 died within 1 month of diagnosis and all 20 died within 3 months. The main reason for patients not receiving chemotherapy was poor clinical status. Those receiving chemotherapy typically received multiple cycles of doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) with/without involved field radiotherapy [37]. Statistically significant predictors of non-treatment were HIV status, BMI, WCC, Hb, platelet count, albumin, LDH, histological subtype and having had a TB work-up done (Wald test: $p < 0.05$). Patients with refractory disease mostly received dexamethasone, high-dose Ara-C and Platinol (DHAP) salvage chemotherapy [38]. Nine HIV sero-positive patients received a haematopoietic stem cell transplant (HSCT), of which one was an allogeneic transplant and eight were autologous transplants.

Outcome and additional associations with overall survival

BMI and HIV positivity, HL-subtype, if a patient received TB therapy or chemotherapy, Hb, platelet count and albumin level all showed a statistically significant impact on 5-year OS (all with $p < 0.001$). In addition, LDH ($p = 0.005$), ESR ($p = 0.04$) and CD4-count ($p = 0.003$) also showed a statistically significant impact on 5-year OS. Gender, age, presenting WCC, cART prior to HL diagnosis and whether a laboratory proven TB organism was demonstrated, had no statistically significant impact on 5-year OS (all with $p > 0.05$).

Discussion

This retrospective analysis of adults with HL showed a 5-year OS for all HL patients of 56%. Outcome was particularly adverse in patients with HIV infection and BMI; moreover, 31% were unable to start chemotherapy due to co-morbidities. In comparison, prospective trials report a 90% 5-year OS [39–42]. One retrospective analysis from the USA reported a 5-year OS of 62% in 79 HIV+ HL patients that received treatment in different facilities between 1996 and 2010 [43]. Another large retrospective analysis of 14 North American cancer registries subsequently confirmed this, by showing a 5-year OS of 63% in HIV+ HL compared to a 5-year OS of 82% in HIV− HL [10]. With the advent of cART and improved supportive care strategies, survival of HIV+ HL patients has improved and is now approaching that of their HIV− counterparts [37, 38, 44–46]. However, prospective clinical trials often exclude less suitable candidates, leading to a selection bias that yield improved survival rates compared to those treated in real life situations, seen outside of structured medical trials [10, 43]. SA is a middle per capita income country with many challenges in health care associated with developing countries [47]. The International Agency for Research on Cancer (IARC) showed a 27% to 29% difference in the 5-year OS of HL between countries with well-developed health services (5-year OS of 74%) and countries with less developed health services (5-year OS of 45%) [48]. Consequently, even though our survival rates are lower when compared to retrospective data from developed nations, they are comparable to other developing countries in Africa, Asia and Central America with similar public sector socio-economic constraints as SA [48].

The BMB plays an important role in developing countries where PET-CT is not widely available and where the diagnosis of HL is frequently made on BMB [25]. In addition, interpretation of PET-CT results remain problematic in the HIV setting due to factors including underlying co-infections, inflammation, and co-existent AIDS-related malignancies (e.g. Kaposi sarcoma) that can cause nodal FDG uptake, leading to false positive PET-CT results [26–28]. Furthermore, the degree of FDG uptake is directly related to HIV-VL, inversely related to the CD4 cell count and it is not possible to clearly distinguish malignancy from tuberculosis (TB) [28]. Resource-poor countries have much higher rates of BMI at diagnosis than first world settings, which we confirmed in this study, demonstrating 28% vs 5% in BMI in the HIV− HL group [17–19] and 61% vs 50% in the HIV+ group [20–24]. BMI had a significant impact on survival for both HIV+ and HIV− patients ($p < 0.001$). Our HIV+ patients with BMI performed very poorly with a 5-year OS of 18%, with more than half of these dying within 3 months of diagnosis.

Histological subtypes appear similar to the international literature with NSCHL predominating in the HIV− group and CHL-unclassified and MCCHL dominating in the HIV+ group [10]. A retrospective analysis of the American National Cancer Data Base from 2002 to 2012 which compared HIV-positive and HIV-negative HL, revealed outcomes to be similar for NSCHL and MCCHL subtypes, but significantly worse in CHL-unclassified [7], which we confirmed in this study; however, this may be due to many of the CHL-unclassified group being diagnosed on BMB and thus having poorer outcomes for that reason.

In this cohort, 29% of newly diagnosed patients with HL were HIV+, which is much higher than a published North American figure of 4% [10]. In contrast to the literature from certain developed nations [37], HIV sero-positivity in our cohort had a statistically adverse association with 5-year OS ($p < 0.001$). However, HIV had no effect on survival in BMI negative patients (5-year OS of 80%) and this group actually

had slightly better outcomes that their HIV-counterparts (5-year OS of 67%). This observation may be due to the small sample size (25/219 patients), or due to the fact that HIV+ patients have more frequent follow-up visits at ARV clinics and thus better care compared to their HIV− counterparts. This finding supports the previous observation that low risk HIV+ patients tend to have similar outcomes to their HIV− counterparts [37]. Among the HIV+ group, 61% (39/64) were on cART when the diagnosis of HL was made, but still had low CD4 counts suggesting poor immune recovery or non-compliance. A recent large multicentre study including 482 HIV+ lymphoma patients from the USA showed a worse OS in those without adequate HIV viral suppression and it was recommended that all HIV-associated lymphomas receive cART in conjunction with chemotherapy [49]. However, adequate HIV-viral suppression did not show a statistical significant effect on OS in the HL subgroup. HIV-viral suppression also failed to show a statistical significant effect on 5-year OS in our study, likely due to the small numbers of cases with adequate data available. Therefore, the impact of viral suppression on OS in HIV-associated HL remains unclear.

Immunosuppression (defined as a CD4 count less than 350 cells/μL) generally confers an increased risk of developing HL in the HIV positive population [50]. Some investigators have not found the CD4 count to be predictive of OS in patients with HIV-associated HL [46, 51], while others did [52, 53]. In this study, the CD4 count had a statistically significant impact on 5-year OS ($p = 0.003$). Similar to another study, which included 29 HIV-associated HL patients from SA, we also showed lower CD4 counts at presentation compared to the international literature [54]. Lower CD4 counts are associated with increased incidence of opportunistic infections in patients with HIV-associated HL [55] which leads to increased mortality [56]. Within the SA context, an estimated 73% of TB cases have concomitant HIV infection [30]. The overlapping signs and symptoms of TB and HL are a major contributor to delayed diagnosis and HL patients presenting with advanced disease. A previous small study from the Gauteng region in SA, showed a high prevalence of TB in patients with HIV-associated HL with 59% (17/29) of HIV-associated HL patients having either active or a past documented TB infection [54]. In our study, 72% of patients with HIV-associated HL had received TB therapy in the year prior to diagnosis and these patients had significantly worse 5-year OS ($p < 0.001$). However, the presence of a laboratory proven TB organism did not affect outcome ($p = 0.6$), but this may be due to low sample numbers.

In view of SA having the highest HIV [3, 4] and the third highest incidence of TB [30] in the world together with the fact that HIV positivity is associated with an increased risk of developing HL [1, 2], it is imperative that clinicians maintain a high index of suspicion for lymphoma in immunocompromised patients presenting with lymphadenopathy, cytopenias and/or B-symptoms, particularly when they do not respond adequately to empiric TB therapy. Prolonged empiric TB therapy and delayed histological diagnosis of HL, compounded by delayed referrals to tertiary health care institutions led to patients presenting with advanced disease with 11% (25/219) of the whole HL group being unfit for chemotherapy (23/25 of these had BMI); all had had a previous TB work-up done and while only 16% (4/25) had laboratory proven TB, 84% (21/25) received TB therapy in the year prior to the HL diagnosis.

This is a likely reason why HIV-associated HL typically presents with more advanced disease than their HIV negative counterparts [46], which is then reflected in the higher BMI rate and lower survival seen in our cohort. Thirty one percent (20/64) of HIV+ patients did not receive chemotherapy.

To the best of our knowledge, this is the first report of 5-year survival outcomes in HL from SA. We confirm the high HIV and TB prevalence in the Western Cape province of SA, together with advanced HL disease-stage at presentation result in adverse outcome, particularly in those with BMI and those unfit to receive chemotherapy.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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