The International Prognostic Score and HIV status predict red cell concentrate transfusion needs in Hodgkin lymphoma.

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Abbreviations

ABVD	Adriamycin, Bleomycin, Vincristine and Darcabazine
ANOVA	Analysis of Variance
ART	Antiretroviral therapy
BEACCOP	Bleomycin, Etoposide, Doxorubicin, Cyclophosphamide, Vincristine, Procarbazine and Prednisone
BM	Bone marrow
BMI	Body mass index
CR	Complete response
CT	Computed Tomography
ECOG	Eastern Cooperative Oncology Group
ESMO	European Society for Medical Oncology
FBC	Full blood count
GSH	Groote Schuur Hospital
Hb	Haemoglobin
HIVVL	HIV viral load
HL	Hodgkin Lymphoma
HL – IPS	Hodgkin Lymphoma International Prognostication Score
HREC	Human Research Ethics Committee
ICMJE	International Committee of Medical Journal Editors
ICTRP	International Clinical Trials Registry Platform
IFRT	Involved field radiotherapy
LN	Lymph node
NCCN	National Comprehensive Cancer Network
NHL	non-Hodgkin lymphoma
NHLS	National Health Laboratory Service
PBM	Patient blood management
PD	Progressive disease
PET	Positron Emission Tomography
PET/CT	[^{18}F]-Fluoro-Deoxy-Glucose Positron Emission Tomography combined with computed tomography
PLT	Platelets

PLWH	People living with HIV
PRD	Primary Refractory Disease
RCC	Red cell concentrate
SA	South Africa
SD	Stable Disease
TB	Tuberculosis
UCT	University of Cape Town
WCBS	Western Cape Blood Services
WHO	World Health Organisation

Title

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Abstract

Despite the burden of anaemia among Hodgkin Lymphoma (HL) patients, data evaluating red cell concentrate transfusion is limited. We retrospectively studied 285 newly diagnosed HL patients who received first-line ABVD treatment at Groote Schuur Hospital, Cape Town. HIV prevalence in the cohort was 39.5% and 74.2% of patients had advanced stage HL. Patient prognosis was scored using the HL International Prognostic Score (IPS-7) and HL IPS-3. Seventy (24.6%) patients were transfused with a median of 2(IQR 1-5) units per patient. Compared to HIV-negative patients, more HIV-positive patients were transfused (14.1% vs 40.4%, P<0.001) and received more units, median 2(IQR 1-3) vs. 3(IQR 2-5), P=0.035. HL IPS-7 (OR 2.1, P<0.001) and HL IPS-3 (OR 2.6, P<0.001) were independently associated with transfusion. HL IPS-7, HL IPS-3 and HIV positivity remained associated with transfusion after adjusting for covariates. For patients with newly diagnosed HL, HL IPS-7, HL IPS-3 and HIV status predicted transfusion.

Introduction

First-line therapy for Hodgkin Lymphoma (HL) with Adriamycin, bleomycin sulfate, vinblastine sulfate, and dacarbazine (ABVD) is associated with excellent long-term survival [1,2]. In sub-Saharan Africa where 71% of people living with HIV (PLWH) resided in 2017, there remains an estimated 15-30-fold increased risk to develop HL in PLWH despite the gradual antiretroviral therapy (ART) rollout in South Africa (SA) since 2004 [3,4]. Compared to high income countries, the majority of HL patients in low- and middle-income countries present at an advanced stage [5-8]. Patient outcomes in a country of similar socioeconomic parity as SA, Brazil, have been reported to be inferior compared to high income countries [7,9,10].

In SA, HIV presentation at an advanced stage is common due to frequent late entry into ART programs [11-13]. In addition to late presentation of HL and HIV, the tuberculosis (TB) and HIV endemic environment creates unique obstacles in the diagnostic pathway of cancers such as HL, with frequent delayed diagnosis due to preemptive TB misdiagnosis [14-16]. A confluence of these factors leads to advanced HL stage at presentation in SA, whether patients are HIV-positive or HIV-negative, and we have shown that HIV-positive HL patients in our centre have significantly poorer outcomes than HIV-negative ones [14,17,18]. This contrasts with findings in high-income countries where HIV status has no influence on outcomes in HL [9,10]. Since 1998, the Hodgkin Lymphoma International Prognostic Score (HL IPS-7) consisting of seven variables (serum albumin, haemoglobin (Hb), male sex, Lugano stage IV disease, age, white cell count and lymphocyte count), has been used to predict freedom from progression in advanced HL [19]. More recently, a simplified prognostic score (HL IPS-3) using only three variables has been introduced, namely: age, Hb and Lugano stage IV disease – these may pose an advantage especially during retrospective analyses [20-21].

In adult HL, the prevalence of anaemia ranges from 40% to 57.4% at diagnosis [22-23]. Anaemia was detected in 84.8% of unselected consecutive HIV-positive patients admitted at a district hospital in Cape Town, South Africa [13-24]. Nevertheless, there is a paucity of data evaluating predictors for red cell concentrate (RCC) transfusion in HL and in quantifying transfusion need during first-line treatment. Moreover, as far as could be ascertained, there are no large-scale direct comparisons of transfusion need in HIV-positive and HIV-negative HL patients. The largest trial to date is the prospective GSHG HD15EPO Trial, not primarily investigating transfusion burden in HL, but rather the impact of epoetin alpha® on transfusion in patients with advanced stage disease during first-line treatment with BEACOPP using a transfusion trigger of Hb<8g/dL [25]. In the erythropoietin arm, 63.3% of patients were transfused while a higher proportion of 72.6% needed transfusion in the placebo arm (P<0.001). We could find no other prospective studies dealing with transfusion in HL. The most comprehensive retrospective data comes from Pakistan, a low-income region, including 481 patients with both non-Hodgkin lymphoma (NHL) and HL where 104 (22.4%) were transfused during one year of observation, 30 of whom had HL (27.8%). Although baseline Hb was significantly lower in the 30 HL patients, NHL patients received significantly more red cell units (3.97 ± 3 in HL versus 6.74 ± 5.69 in NHL) [24].

Analysis of red cell utilization in a well-characterized HL cohort provides the opportunity to measure the magnitude of transfusion need in newly diagnosed HL patients on first-line ABVD treatment. We conducted a retrospective cohort study of adolescent and adult HL patients diagnosed from 2010 to 2019 in our tertiary care Clinical Haematology unit at Groote Schuur Hospital (GSH). We described the baseline clinical characteristics of our cohort and analyzed factors contained in HL IPS-7 and HL IPS-3, as well as HL subtype, performance status, B

symptoms and bone marrow involvement, for association with red cell transfusion in both HIV-positive and HIV-negative HL patients on first-line treatment.

Materials and Methods

Study Design and Participant Selection

Patients consecutively diagnosed with and treated for classical HL from 2010 to 2019 in the adult Haematology and Oncology units at Groote Schuur Hospital (GSH) in the Western Cape region of SA, were included in this retrospective cohort study of patients aged 13 years and older. In this region, the policy is to treat patients in adult units from 13 years onwards. GSH is a 970-bed tertiary referral academic treatment centre affiliated with the University of Cape Town.

Demographic and Clinical Data

Baseline characteristics were acquired from paper and electronic medical records. Patient age, sex and B symptoms were assessed. The Eastern Cooperative Oncology Group (ECOG) performance status scale was used to assess functional status [26]. *Diagnosis*: Classical HL was subtyped on lymph node (LN) specimens: nodular sclerosis, mixed cellularity, lymphocyte-rich, lymphocyte depleted and HL unspecified according to the revised 2016 WHO Classification [27]. *Imaging for staging at baseline*: Computed Tomography (CT), and [^{18}F]-Fluoro-Deoxy-Glucose Positron Emission Tomography combined with computed tomography (PET/CT) imaging data was obtained from the IntelliSpace® PACS Enterprise and NUcMED® systems, Western Cape Hospitals repositories for radiological patient data. PET/CT had limited availability due to logistical and resource constraints. *Staging:* Since 2014 the Lugano classification was used for initial staging of patients [28]. Patients staged according to the Ann Arbor classification before

2014, were reviewed for the present study according to the 2014 Lugano classification. We base our institutional treatment protocol on the National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO) guidelines for clinical risk classification, to derive limited (early favourable) and intermediate (early unfavourable) disease categories for patients in stage I and II. Patients in stage III and IV are classified as advanced stage disease [29,30]. *Prognostication:* The risk factors contained in the HL IPS-7 and HL IPS-3 were applied to all patients [19,21]. *Study period and blood utilization*: The duration of investigation included a period of six months prior to diagnosis until completion of first-line chemotherapy to the point of clinical recovery from the last chemotherapy or radiotherapy. Blood product usage data during this period was quantified from the Western Cape Blood Services (WCBS) database. The trigger for red cell transfusion in the local health care environment was Hb < 8g/dL and there were no restrictions on access to transfusion. *Bone marrow evaluation:* Bone marrow involvement (BMI) was evaluated, depending on availability, using either PET/CT imaging or bone marrow biopsy, or both. *Treatment*: Patients received first-line treatment with ABVD chemotherapy with or without involved field radiotherapy (IFRT). Our institutional protocol is derived from the NCCN and ESMO guidelines within the bounds of local resource constraints. [29]. ART therapy was concomitantly administered with chemotherapy. *Laboratory results*: Results of diagnostic biopsies and bone marrow (BM) histology, blood biochemistry, Full Blood Count (FBC), plasma HIV viral load (HIVVL) and CD4 cell counts were retrieved from the National Health Laboratory Service (NHLS). CD4 cell counts and HIVVL tested three months prior to and two weeks after diagnosis were accepted for inclusion in the study. HIV-positive patients were either classified as *HIV-positive poorly controlled* (not virally suppressed on ART failing treatment, or newly diagnosed

not on treatment), or *HIV-positive well controlled* (on ART and virally suppressed), using a HIVVL cut-off of <50 copies/ml.

Statistical Analysis

Categorical variables were described by frequencies and percentages while continuous variables were described by means and standard deviations (parametric data) or medians and interquartile ranges (non-parametric data). Categorical variables were compared in those who were transfused and those who were not transfused using Pearson Chi-squared or Fisher's exact tests, as appropriate. Continuous variables were compared using student's t-tests or ANOVA (parametric data) and Mann-Whitney or Kruskal Wallis tests (non-parametric data). Univariable and multivariable logistic regression models were used to investigate the associations between RCC transfusion status and covariates. Covariates assessed included the components and their predetermined cut-off values used to calculate the HL IPS-7 or HL IPS-3 (age, sex, albumin, Hb, Lugano stage, white blood cell count, and absolute lymphocyte count) [19], HL IPS-7 and HL IPS-3 numerical values and three additional factors: HIV status, B symptoms and ECOG performance status. Four multivariable models were developed; one including the seven components of the HL IPS-7 with the additional factors; second including the HL IPS-7 score with the additional factors; third including the three HL IPS-3 components with the additional factors; and forth including the HL IPS-3 score and the additional factors. Data were analyzed using STATA version 14.0 (StataCorp Inc, College Station, Texas, USA). A *P*-value <0.05 was considered statistically significant. Ethics approval was obtained from UCT Human Research Ethics Committee (HREC 306/2020) and GSH ethics review board.

Results

A total of 285 patients were diagnosed with and treated for HL from 2010 to 2019 at GSH shown in Table 1. The median age was 34.5 years and 62.9% of patients were male. An ECOG >2 was recorded in 35% of patients while B symptoms were observed in 81%. The majority of patients (75.6 %) had advanced disease according to the modified Lugano criteria at presentation. BM involvement was present in 110 (70.5%) of 156 patients with Lugano stage IV disease, of which 94 (85.5%) were verified on trephine biopsy and 16 (14.5%) were based solely on the PET report. HIV prevalence at diagnosis was 39.5%, with one third of HIV-positive patients having poorly controlled HIV. Of the 35 patients with poorly controlled HIV, 28 (80.0%) were ART naïve at diagnosis, and 7 (20.0%) had virological failure on ART.

Among the 285 patients, 70 (24.6%) were transfused with RCC. Figure 1 shows the distribution of RCC units transfused by HIV status. Transfusion was more frequent in HIV-positive patients regardless of HIV control status. Significantly, more HIV-positive patients (40.4%) were transfused than HIV-negative patients (14.1%) (P<0.001). The median number of transfusions for all patients was 2 (IQR 1-5); 2 units (IQR 1-3) for HIV-negative, and 3 units (IQR 2-5) for HIV-positive patients (P=0.035). Significantly more patients who were transfused had advanced stage disease, BM involvement, B symptoms and ECOG >2 (Table 1). The distribution of HL subtypes differed significantly by transfusion status while age and sex did not (P=0.001). Those who had a transfusion also had significantly lower Hb, albumin, white cell count and absolute lymphocyte count at diagnosis as well as a higher median HL IPS-7 and HL IPS-3 compared to their counterparts. The distribution of HL IPS-7 and HL-IPS-3 in the total cohort and by transfusion status are presented in Figures 2 (A) and (B), respectively. Distributions differed by transfusion status with those who were transfused having higher scores for both HL IPS-7 and HL-IPS-3.

Univariable and multivariable models evaluating associations between transfusion status and covariates are presented in Table 2. In univariable analysis, the HL IPS-7 components aside from age and sex were associated with an increased odds of being transfused. Both the HL IPS-7 and HL IPS-3 scores as well as the three additional factors (HIV positivity, B symptoms and ECOG 3-4) were also independently associated with transfusion (Table 2). Every one-point increase in HL IPS-7 was associated with a 2-fold increase in the odds of transfusion while every one-point increase in HL IPS-3 was associated with a 2.5-fold increase in transfusion odds. In multivariable analyses including HL IPS-7 components and additional factors, Albumin<40g/dL, Lugano stage IV and well controlled HIV-positive status were significantly associated with an increased odds of transfusion, after adjusting for all other covariates (model 1). When the HL IPS-7 score and the three additional factors were modelled together, HL IPS-7 and HIV positivity were significantly associated with transfusion after adjusting for B symptoms and ECOG (model 2). In multivariable analyses including HL IPS-3 components and additional factors, Hb<10.5 g/dL, Lugano stage IV and HIV positivity were significantly associated with transfusion, after adjusting for other covariates (model 3). When the HL IPS-3 score and the three additional factors were modelled together, HL IPS-3 and HIV positivity were significantly associated with transfusion after adjusting for B symptoms and ECOG (model 4).

There was a positive correlation between albumin and Hb (r=0.709) (Supplementary Figure 1) and Hb <10g/dL was significantly associated with having a transfusion, regardless of HIV status (Supplementary Table 1).

Table 1: Characteristics of patients treated for Hodgkin Lymphoma from 2010 to 2019 at Groote Schuur Hospital and according to red cell concentrate transfusion status

CHARACTERISTIC	TOTAL POPULATION (N=285) Col %, median (IQR) or mean (SD)	RCC TRANSFUSED (n=70, 24.6%) Row%, median (IQR) or mean (SD)	RCC NOT TRANSFUSED (n=215, 75.4%) Row %, median (IQR) or mean (SD)	*p*-value
Age at diagnosis	34.5 (27.0-44.7)	35.8 (28.5-42.0)	34.3 (26.3-45.3)	0.736
Sex				
Male	156 (54.7)	44 (28.2)	112 (71.8)	0.116
Female	129 (45.3)	26 (20.2)	103 (79.8)	
HIV status (n=281)				
HIV-positive (Poorly controlled)	35 (12.5)	14 (40.0)	21 (60.0)	<0.001
HIV-positive (Well controlled)	76 (27.0)	30 (39.5)	46 (60.5)	
HIV-negative	170 (60.5)	24 (14.1)	146 (85.9)	
Stage at diagnosis (n=279)				
Limited	15 (5.4)	3 (20.0)	12 (80.0)	
Intermediate	53 (19.0)	4 (7.6)	49 (92.5)	0.002
Advanced	211 (75.6)	61 (28.9)	150 (71.1)	
Bone Marrow Involvement (n=268)				
Involved	110 (41.0)	47 (42.7)	63 (57.3)	<0.001
Not Involved	158 (59.0)	20 (12.7)	138 (87.3)	
Haemoglobin (g/dL) (n=279)	10.3 (7.9-12.4)	7.4 (6.5-8.9)	10.9 (9.3-12.8)	<0.001
Albumin at diagnosis (g/dL) (n=218)	36.0 (26.0-41.0)	25.0 (19.0 -30.0)	38.0 (32.0-42.0)	<0.001
White cell count ($x10^9$/L) (n=279)	8.0 (4.6-12.7)	4.8 (2.5-9.0)	8.9 (5.4-13.4)	<0.001
Lymphocyte count ($x10^9$/L) (n=261)	1.3 (0.7-2.0)	0.7 (0.4-1.2)	1.5 (0.9-2.3)	<0.001
ECOG (n=244)				
ECOG 1 and 2	159 (65.2)	33 (20.8)	126 (79.3)	0.022
ECOG > 2	85 (34.8)	29 (34.1)	56 (65.9)	
B Symptoms (n=268)				
Present	217 (81.0)	58 (26.7)	159 (73.3)	0.010
Absent	51 (19.0)	5 (9.8)	46 (90.2)	
Histological types				
Nodular sclerosing	143 (50.2)	25 (17.5)	118 (82.5)	0.001
Mixed cellularity	34 (11.9)	4 (11.8)	30 (88.2)	
Lymphocyte-rich	6 (2.1)	2 (33.3)	4 (66.7)	
Lymphocyte depletion	5 (1.8)	2 (40.0)	3 (60.0)	

HL unspecified	97 (34.0)	37 (38.1)	60 (61.9)	
HL IPS-7 (n=200)	3 (2-4)	4 (4-5)	2 (1-4)	<0.001
HL IPS-3 (n=274)	1 (1-2)	2 (1.5-2)	1 (1-2)	<0.001

IQR: Interquartile range; SD: standard deviation; ECOG: Eastern Cooperative Oncology Group; HIV: Human Immunodificiency Virus; RCC: red cell concentrate; HL IPS: Hodgkin Lymphoma International Prognostic Score

Table 2: Univariable and multivariable logistic regression analysis investigating the associations between red cell concentrate transfusion status and covariates.

	Univariable			Multivariable model 1 (n=169)			Multivariable model 2 (n=169)			Multivariable model 3 (n=227)			Multivariable model 4 (n=227)		
CHARACTERISTIC	**OR**	**95% CI**	***p*-value**	**OR**	**95% CI**	***p*-value**	**OR**	**95% CI**	***p*-value**	**OR**	**95% CI**	***p*-value**	**OR**	**95% CI**	***p*-value**
Age							-	-	-				-	-	-
<45 years	ref			ref						ref					
≥45 years	0.7	0.4-1.4	0.345	0.5	0.2-1.5	0.192				0.6	0.2-1.5	0.260			
Sex							-	-	-				-	-	-
Female	ref			ref						-	-	-			
Male	1.6	0.9-2.7	0.117	2.4	0.9-6.1	0.077									
Albumin							-	-	-				-	-	-
≥40	ref			ref						-	-	-			
<40 g/dL	38.8	5.2-287.3	<0.001	12.4	1.4-107.1	0.022									
Haemoglobin							-	-	-				-	-	-
≥10.5 g/dL	ref			ref						ref					
<10.5 g/dL	7.5	3.7- 15.0	<0.001	2.9	1.0-8.8	0.061				4.3	2.0-9.4	<0.001			
Lugano stage							-	-	-				-	-	-
Stage I-III	ref			ref						ref					
Stage IV	4.6	2.3-9.2	<0.001	4.0	1.1-14.5	0.036				2.8	1.2-7.0	0.025			
White blood cells							-	-	-	-	-	-	-	-	-
<15x10^9 cells/L	ref			ref											
≥15x10^9 cells/L	0.4	0.2-1.0	0.059	0.5	0.1-2.3	0.378									
Lymphocytes										-	-	-	-	-	-
≥0.6x10^9 cells/L	ref			ref			-	-	-						
<0.6x10^9 cells/L	4.3	2.2-8.4	<0.001	2.4	0.8-6.8	0.117									
HL – IPS 7 score	2.1	1.6-2.8	<0.001	-	-	-	2.1	1.4-2.9	<0.001	-	-	-	-	-	-
HL – IPS 3 score	2.6	1.8-3.7	<0.001	-	-	-	-	-	-	-	-	-	2.1	1.3-3.3	0.001
HIV status															
Negative	ref			ref			ref			ref			ref		
Positive (poorly controlled)	4.1	1.8-9.0	0.001	2.5	0.6-10.1	0.214	5.4	1.5-18.8	0.009	3.0	1.1-8.4	0.036	4.2	1.6-11.4	0.004
Positive (well controlled)	4.0	2.1-7.5	<0.001	2.9	1.0-8.0	0.043	5.2	2.1-12.7	<0.001	2.7	1.3-5.8	0.011	3.3	1.6-6.9	0.001
B symptoms															
Absent	ref			ref						ref			ref		
Present	3.4	1.3-8.9	0.014	1.5	0.2-9.5	0.657	1.9	0.4-9.9	0.435	1.2	0.4-3.8	0.807	1.3	0.4-4.0	0.640
ECOG															
1-2	ref			ref			ref			ref			ref		
3-4	2.0	1.1-3.6	0.024	1.0	0.4-2.6	0.987	1.0	0.4-2.3	0.980	1.1	0.5-2.3	0.806	1.2	0.6-2.5	0.561

ECOG, Eastern Cooperative Oncology Group; HIV, Human Immunodeficiency Virus; HL IPS, Hodgkin Lymphoma International Prognostication Score; Ref, reference group

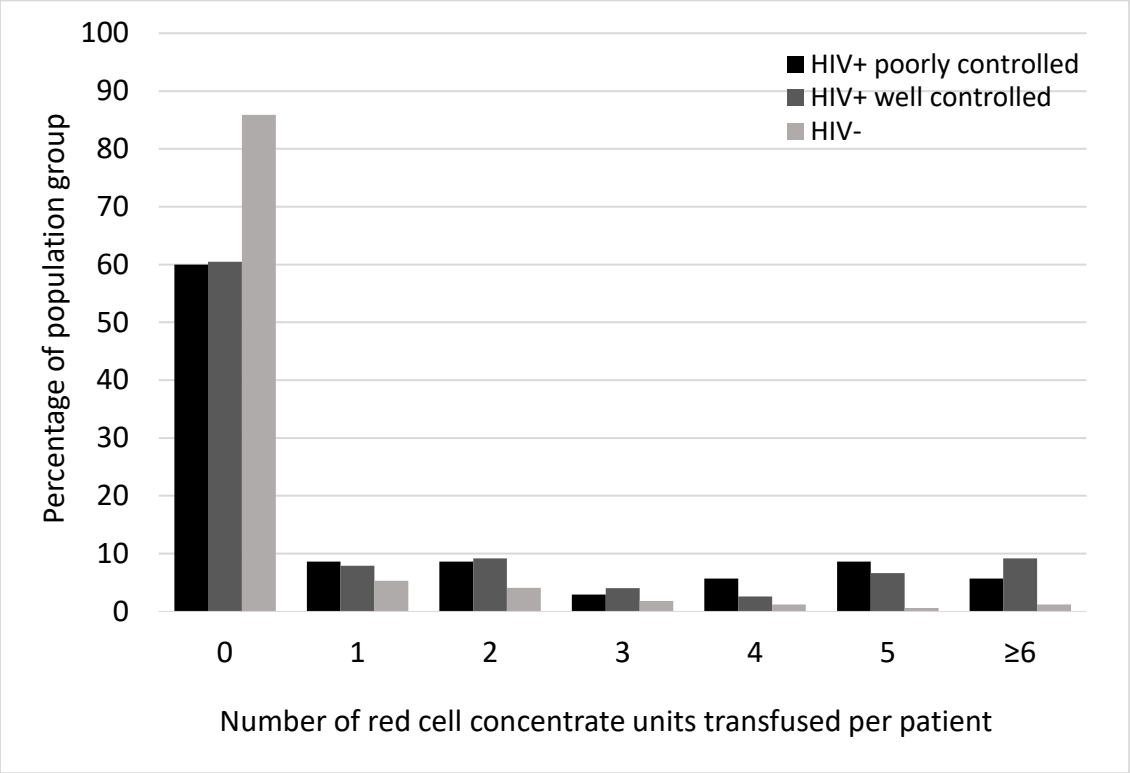

Figure 1: Percentage of population per number of red cell concentrate units transfused.
HIV+, Human Immunodeficiency Virus positive HIV-, Human Immunodeficiency Virus negative

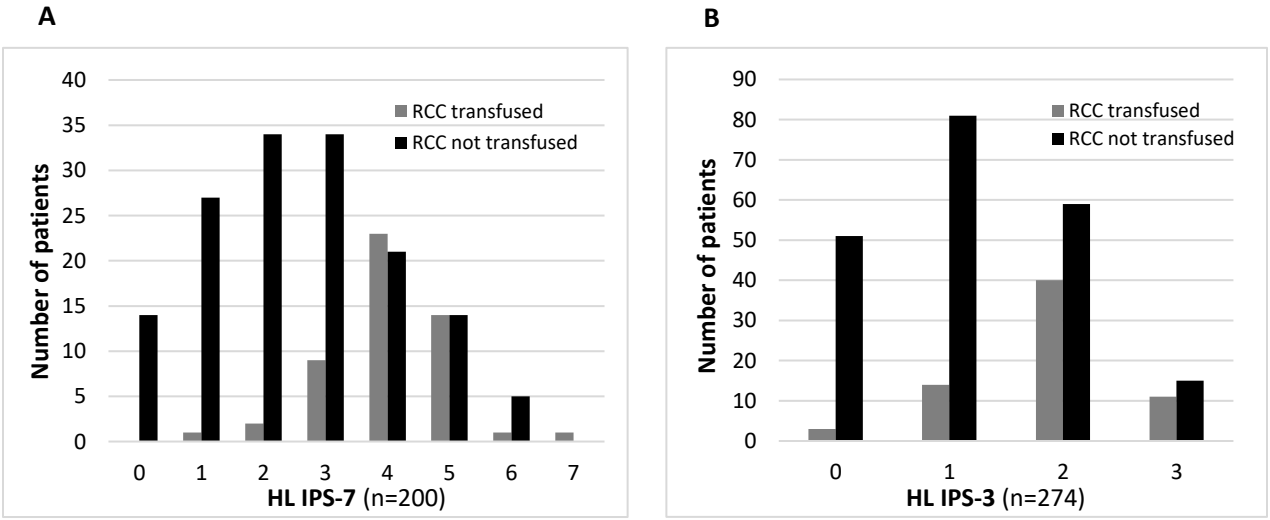

Figure 2: Distribution of HL IPS-7 (A) and HL-IPS-3 (B) in the total cohort and by transfusion status.
RCC, red cell concentrate, HL IPS, Hodgkin Lymphoma International Prognostication Score

Discussion

In this real-world retrospective study reviewing transfusion characteristics among a well-characterized HL cohort during first-line treatment with ABVD, a quarter of patients received at least one unit of RCC. Additionally, this cohort carried a high HIV burden. Each one-point increase in the numerical value of the HL IPS-7, a prognostic score for advanced disease [19] was associated with a 2-fold increase in the odds of having a RCC transfusion. Patients were stratified using the HL IPS because the majority of stage 1 and 2 patients had disease with poor risk factors similar to the patients treated as advanced disease in the original study by Hasenclever and Diehl [19]. Similar results were observed with HL IPS-3 [21]. Additional to both the HL IPS-7 and HL IPS-3, HIV-positivity was associated with transfusion with almost three times more HIV-positive patients (40%) receiving transfusion than HIV-negative patients (14%). This increased transfusion need also holds true for medical inpatients in the HIV endemic setting due to the multifactorial nature of anaemia in HIV [31,32].

The prospective data we have on transfusion incidence in HL is limited to the aforementioned GSHG HD15EPO Trial [25]. In this trial, the advanced stage of patients and the similar transfusion trigger, is comparable to our HIV-negative cohort. For this trial, the median number of transfusions in the placebo group was four per patient, and 72.6% were transfused. In stark contrast, the median number of transfusions in our HIV-negative cohort was two per patient and 14% were transfused. With a similar transfusion trigger, this is unlikely to be explained by differences in transfusion practice and may rather reflect the more intensive marrow suppression of BEACOPP compared to ABVD. In a systematic review analysing the outcomes in five trials of escalated BEACOPP versus ABVD for the treatment of limited and advanced stage HL, significant WHO grade III or IV anaemia was increased by 10-fold (23.6% vs 2.2%) in the 1308 patients who received escalated

BEACOPP compared to the 1117 patients receiving ABVD (RR=10.67, CI 7.14-15.93) [33]. These trials give substantive data on the unequal burden of anaemia during first-line treatment with BEACOPP vs ABVD. However, for the burden of transfusion associated with these two treatments, we could find no further published data and we present here for the first time a study that quantifies this burden for a predominantly advanced stage HL cohort receiving ABVD in the HIV endemic setting [34]. In this cohort, 41% of patients had BM involvement which is similar to other studies conducted in resource limited settings, whereas in developed countries a lower BM involvement ranging from 5.2% to 19% is described [17,35-38]. Advanced stage disease due to diagnostic delay contributed to transfusion need before and after the HL diagnosis [14].

Two variables in the HL IPS-7, namely albumin and Hb, were associated with transfusion. In particular, albumin, which was closely related with Hb at diagnosis, was significantly lower in patients requiring transfusion [39]. This positive correlation between albumin, a negative acute phase reactant and Hb are an indication that liver function and BM reserve both reflect overall metabolic status and the degree of inflammation related to HIV and the lymphoma. Compared to HL IPS-7, Lugano stage IV in the HL IPS-3 was associated with transfusion. The HL IPS-3 is simple, requires fewer variables compared to the HL IPS-7 in predicting transfusion requirements, and is also convenient for retrospective data analysis where components of the HL IPS-7 might not be available [20]. BM involvement at diagnosis is reflected in the IPS Lugano stage variable, and as expected is associated with a higher transfusion need most strikingly seen in the HIV-positive category [37]. Among patients with BM as the initial HL diagnosis, a high proportion were HIV-positive which is usually associated with late diagnosis and cytopenias.

This study is limited by its retrospective nature , and our limited focus on ruling out cases for other causes of anaemia, for example, a formal assessment of iron deficiency was not consistently

performed in all patients. There may have been a confounding effect of competing risk, as patients with more advanced disease might have experienced earlier treatment failure, leading to lower RCC transfusion requirements compared to those without early mortality. Although the commonly held transfusion threshold in our institution at the time of study was an Hb<8 g/dL, this was not prospectively controlled. Lastly, despite a positive correlation between albumin and Hb, both were included in the multivariable analysis as categorical variables. This was because they are both components of HL IPS-3 and HL IPS-7 but we note that this could potentially have reduced model precision. Strengths of our study include the large cohort with complete baseline characteristics of consecutively diagnosed and treated patients from a single centre.

In conclusion, we provide evidence that by first applying the HL IPS and then, HIV status, to the newly diagnosed HL patient in our setting, we can predict the likelihood of transfusion. The simplified HL IPS-3 is as predictive of transfusion as the HL IPS-7. Future prospective studies in HL should examine anaemia etiology and Hb thresholds for transfusion, ideally on a multicenter basis. Implementing better measures for patient blood management in this patient group may decrease transfusion need [32]. Future studies might also examine whether RCC transfusion are independently associated with patient outcomes after controlling for transfusion indication and prognostic indicators.

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Disclosure of Interest Statement

The authors report there are no competing interests to declare.

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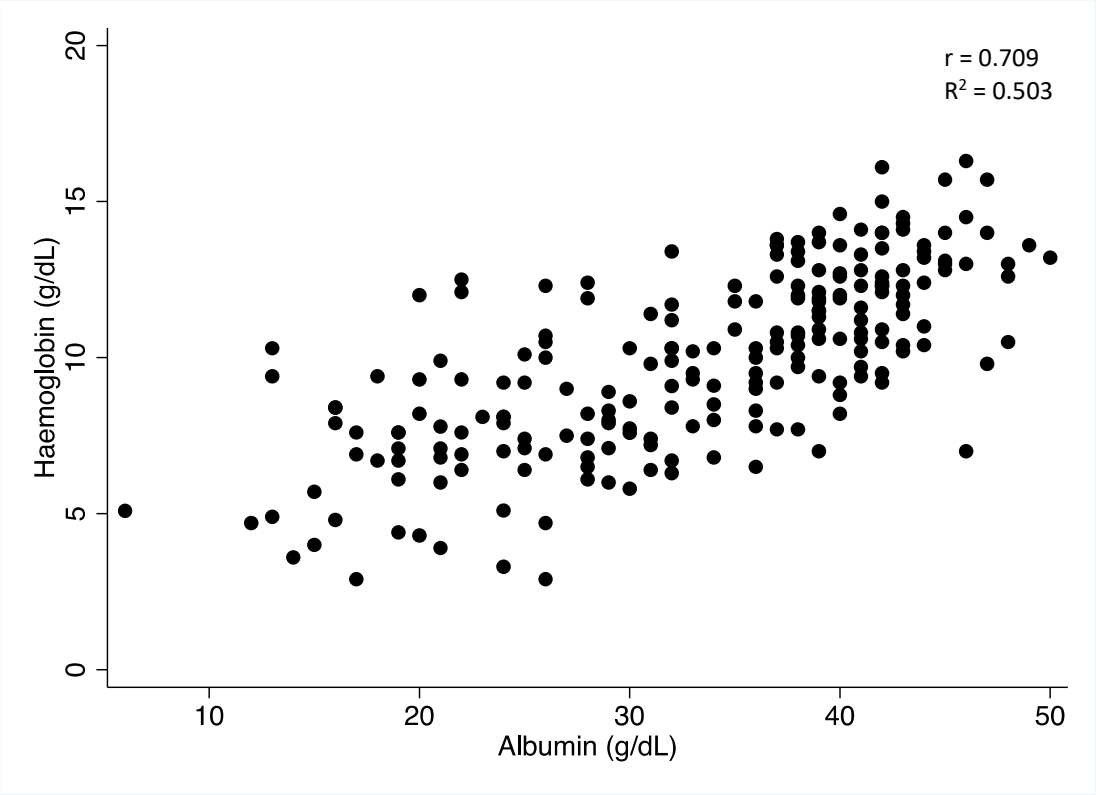
Supplementary Tables and Figures



Supplementary Figure 1: Correlation between Albumin (g/dL) and Hb (g/dL)

Supplementary Table 1: Number (%) of patients transfused and not transfused by haemoglobin level, in all patients and stratified by HIV status.

	Haemoglobin	**Transfused**	**Not transfused**	***P*-value**
All patients	<10 ≥ 10	58 (84.1) 11 (15.9)	67 (31.9) 143 (68.1)	<0.001
HIV+	<10 ≥ 10	39 (84.8) 7 (15.2)	32 (47.8) 35 (52.2)	<0.001
HIV-	<10 ≥ 10	19 (82.6) 4 (17.4)	35 (24.7) 107 (75.4)	<0.001

Appendices

Ethics Approval letter

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room G50- Old Main Building
Groote Schuur Hospital
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18 June 2020

HREC REF:306/2020

A/Prof E Verburgh
Division of Clinical Haematology
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Email: Estelle.verburgh@uct.ac.za
Student: smbkud001@myuct.ac.za

Dear A/Prof Verburgh

PROJECT TITLE: FACTORS INFLUENCING EARLY OUTCOMES AND TRANSFUSION REQUIREMENTS AMONG PATIENTS ON TREATMENT FOR HODGKIN'S LYMPHOMA IN AN HIV BURDENED TERTIARY INSTITUTION-MASTERS CANDIDATE-DR KUDAKWASHE SIMBA-sub-study linked to RR024/2018

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19, dated 17 March 2020.

Approval is granted for one year until the 30 June 2021.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the student: Dr Kudakwashe Simba will also be involved in this study.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator must obtain appropriate institutional approval, where necessary, before the research may occur.

Please quote the HREC reference number in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
NHREC-registration number: REC-210208-007

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

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