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The diffuse large B cell lymphoma disease human immunodeficiency virus Rituximab with Cyclophosphamide hydroxydaunorobic hydrochloride oncovin and prednisone Charlotte Maxeke Johannesburg Academic Hospital non Hodgkin lymphomas

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The diffuse large B-cell lymphoma disease profile at Charlotte Maxeke Johannesburg Academic Hospital from July 2020 to June 2022

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Background: Diffuse large B-cell lymphoma (DLBCL) is one of the most common non-Hodgkin lymphomas (NHL) in adults, and there is limited clinical data available for patients treated in low-resource settings with a high human immunodeficiency virus (HIV) infection burden.

Aim: This article describes the disease burden, clinical presentation and treatment outcomes for DLBCL.

Setting: The study was conducted at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH).

Methods: The study retrospectively reviewed 58 hospital treatment records of patients with DLBCL treated at CMJAH Medical Oncology Clinic from July 2020 to June 2022.

Results: The study had 37 (63.8%) male patients and 21 (36.2%) female patients. The median age was 48 and 49 years for male patients and female patients, respectively, with 44 (75.9%) patients being HIV-positive. Most, 43 (74.1%), received Rituximab with Cyclophosphamide, hydroxydaunorubicin hydrochloride, oncovin and prednisone (R-CHOP) as first-line therapy. Overall survival was 78.2% at year one and 53.1% by year three post-treatment. In the HIV-positive population, the survival was 78.3% at year one and 51.6% at year three.

Conclusion: Diffuse large B-cell lymphoma occurs in a younger population group than previously described. Those with HIV infection are significantly more likely to present with advanced disease and poor overall outcomes.

Contribution: The increasing data on DLBCL in South Africa provide insights that could potentially improve outcomes for this disease.

Keywords: diffuse large B-cell lymphoma; human immunodeficiency virus; Rituximab with Cyclophosphamide, hydroxydaunorubicin hydrochloride, oncovin and prednisone; Charlotte Maxeke Johannesburg Academic Hospital; non-Hodgkin lymphomas.

Introduction

Aggressive B-cell lymphomas are a vast class of cancers that can develop at various stages during the development and maturation of the cell of origin. Diffuse large B-cell lymphoma (DLBCL) is a distinct histological subtype of B-cell lymphomas. The worldwide incidence of DLBCL is approximately 150 000 new cases per year, representing at least 30% of all non-Hodgkin lymphomas (NHL) from the West and more than 40% from Asia.[1,2] The noted median age of presentation is above 60 years.[2] In 2019, NHL was the eighth most frequent malignancy in South Africa.[3] Diffuse large B-cell lymphoma is particularly common in areas of high human immunodeficiency virus (HIV) burden.[4] In the HIV-positive population, lymphomas constitute a third of all HIV-related malignancies.[5] In developed countries, the frequency of DLBCL is reduced within the HIV-positive population because of the use of antiretroviral therapy (ART); however, this has not been established within our local hospital population.[6] Other risk factors include genetic features, immune factors, the Kaposi Sarcoma virus, the Epstein-Barr virus, and occupational and environmental exposures.[1,2]

The molecular sub-sets in DLBCL play a major part in disease biology, prognosis and genomic alteration.[7] Molecular subtypes of particular significance include germinal centre B-cell and activated B-cell subtypes, whereas 10% – 15% remain ambiguous.[8] Chronic B-cell receptor signalling and NFkB activation characterise the activated B-cell subtype. The germinal B-cell is

unique because it exhibits a genetic code typically found in the germinal centre of B-cells.[9] Of note, the activated B-cell subtype has a 3-year progression-free survival of approximately 40% – 50%, in contrast to the germinal B-cell subtype, which is approximately 75%.[9] Within the public sector in South Africa, the germinal centre B-cell is found to occur more commonly in the HIV-positive group of patients.[6]

Since 1995, the regimen best preferred for DLBCL in developed countries has been combination immunochemotherapy comprising Rituximab with Cyclophosphamide, hydroxydaunorubicin hydrochloride, oncovin and prednisone (R-CHOP). Other regimens, such as dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin and rituximab (DA-EPOCH-R), have better progression-free survival in patients with double-hit or triple-hit lymphoma but not in DLBCL.[2]

There has been no proven role for consolidative radiation therapy post-chemotherapy in individuals who have shown a complete metabolic outcome on positron emission tomography-computed tomography (PET-CT). It is, however, of use in cases of residual disease at sites that are amenable to radiotherapy.[10] Approximately 10% – 15% of patients who receive R-CHOP will demonstrate insufficient response or relapse in less than 6 months of treatment, while 20% – 25% of patients will relapse within 2 years of initial successful treatment.[2] Salvage chemotherapy of choice is vast, clinician-dependent and resource-dependent, with the different regimens generally achieving similar outcomes. In patients who have refractory cancer or relapse, utilising chemotherapy with autologous stem cell transplant improves outcomes and sometimes provides a cure.[2]

It is essential to collate the data available within our population and elucidate factors contributing to treatment outcomes.

The study aimed to describe the disease burden, clinical presentation and treatment outcomes for DLBCL at the Medical Oncology Clinic of Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) from July 2020 to June 2022.

Methods

Study design and setting

This retrospective study examined DLBCL patients treated at the Medical Oncology clinic area 495 Charlotte Maxeke Johannesburg Academic Hospital from July 2020 to June 2022.

Study population

All the patients included in the study had a histological diagnosis of DLBCL. They were 18 years or older, had an initial staging scan in the form of either a CT or PET-CT scan, and received a minimum of four cycles of immunochemotherapy. Patients diagnosed with other lymphomas were excluded from the study. Patients were manually searched from a headcount register from July 2020 to June 2022, and records were retrieved from the filing units.

Data collection

Information on patient demographics, risk factors, co-morbidities, clinical characteristics, histological subtype, treatment received and response, radiological imaging results, biochemistry and outcome were all collected from patient hospital records. The information was captured onto a data collection sheet with an assigned unique identity number and tabulated onto an Excel spreadsheet. Overall survival was defined as the time from the date of diagnosis until death.

Treatment of diffuse large B-cell lymphoma

The majority of patients received R-CHOP as their initial chemotherapy unless the treating physician decided upon a more suitable regimen. Intrathecal chemotherapy was given to suspected high-risk patients for central nervous system (CNS) disease. All patients referred to the Medical Oncology clinic had baseline investigations, including a staging CT. Response to treatment was assessed clinically and with interval PET-CT or CT. Patients with refractory or relapsed disease received a second-line chemotherapy agent. Patients with residual disease, amenable to radiotherapy, were referred to the Department of Radiation Oncology for assessment and treatment. The referral hospital managed the co-morbidities of patients.

Analysis

This retrospective study used descriptive statistics and frequency tables to describe clinical and demographic parameters. Means and their standard deviations were used to summarise normally distributed continuous data. Medians and interquartile ranges (IQR) presented continuous, skewed data. Numbers and percentages were used to summarise categorical data. The data compared survival by sex and HIV status. Survival was visualised on the Kaplan–Meier plots, and survival curves were compared using the log-rank test. The Student *t*-test was used to compare means from normally distributed continuous variables, and the Wilcoxon rank-sum test was used to compare medians from non-normal continuous data. Statistical significance was considered at a p-value < 0.05. Stata Corp. MP Version 17 was used to compute the statistical data (College Station, Texas, United States).

Ethical considerations

This study was approved by the University of the Witwatersrand Human Research Ethics Committee on 15 November 2023 (reference number: M230612 MED23-05-058). The authors created a reference list that included the patient's hospital number and an assigned study number. Once entered into the study dataset, participants could only be identified by their study number. To maintain patient confidentiality, the reference list was accessible only to the

principal investigator. All patient identifiers were removed once the project transitioned to the data analysis phase.

Results

A total of 58 patients were diagnosed with DLBCL, comprising 37 male patients (63.8%) and 21 female patients (36.2%) (Table 1). The majority were of black African descent (77.6%). Median age was similar between sexes: 48 years for male patients (IQR 42–53) and 49 years for female patients (IQR 43–52) (Table 1). HIV infection was present in 75.9% (44/58), with 37.9% (22/58) having CD4 counts < 200 cells/μL and 39.7% (23/58) with viral loads > 50 copies/mL (Table 1).

The most common histological subtype was germinal centre B-cell (50.0%), and the predominant stage at initial CT

TABLE 1: Demographic and clinical characteristics of patients treated for diffuse large B-cell lymphoma by sex.

Variable	Male patients				Female patients				Total			
	n = 37 (63.8%)				*n* = 21 (36.2%)				*N* = 58 (100%)			
	n	%	Median	IQR	*n*	%	Median	IQR	*n*	%	Median	IQR
Age (years)	-	-	48	42–53	-	-	49	43–52	-	-	49	42–53
18–28	2	5.4	-	-	0	0.0	-	-	2	3.5	-	-
29–38	4	10.8	-	-	3	14.3	-	-	7	12.1	-	-
39–48	13	35.1	-	-	6	28.6	-	-	19	32.8	-	-
49–58	12	32.4	-	-	9	42.9	-	-	21	36.2	-	-
59–68	3	8.1	-	-	2	9.5	-	-	5	8.6	-	-
69+	3	8.1	-	-	1	4.8	-	-	4	6.9	-	
Race												
Black people	27	73.0	-	-	18	85.7	-	-	45	77.6	-	-
White people	9	24.3	-	-	3	14.3	-	-	12	20.7	-	-
Indian people	1	2.7	-	-	0	0.0	-	-	1	1.7	-	-
HIV CD4 count (cells/μL)												
< 200	11	29.7	-	-	11	52.4	-	-	22	37.9	-	-
> 200	13	35.1	-	-	4	19.1	-	-	17	29.3	-	-
HIV viral load (copies/mL)												
< 50	10	27.0	-	-	4	19.1	-	-	14	24.1	-	-
> 50	12	32.4	-	-	11	52.4	-	-	23	39.7	-	-
HIV treatment regimen												
TLD	15	40.5	-	-	10	47.6	-	-	25	43.1	-	-
TEE	10	27.0	-	-	5	23.8	-	-	15	25.9	-	-
ALD	1	2.7	-	-	0	0.0	-	-	1	1.7	-	-
Non-HIV risk factors	30	81.1	-	-	18	85.7	-	-	48	82.8	-	
Smoking	3	8.1	-	-	0	0.0	-	-	3	5.2	-	-
EBV	0	0.0	-	-	1	4.8	-	-	1	1.7	-	-
No comorbidities	24	64.9	-	-	16	76.2	-	-	40	69.0	-	-
Diabetes	1	2.7	-	-	0	0.0	-	-	1	1.7	-	-
Diabetes and hypertension	3	8.1	-	-	0	0.0	-	-	3	5.2	-	-
Diabetes, hypertension and Ischaemic heart disease	2	5.4	-	-	0	0.0	-	-	2	3.5	-	-
Hypertension	3	9.4	-	-	0	0.0	-	-	3	6.0	-	-
Hypothyroidism and Parkinson's	1	2.7	-	-	0	0.0	-	-	1	1.7	-	-
Hepatitis B	1	2.7	-	-	3	14.3	-	-	4	6.9	-	-
Chronic kidney disease	1	2.7	-	-	0	0.0	-	-	1	1.7	-	-
Histology												
Germinal centre	19	51.4	-	-	10	47.6	-	-	29	50.0	-	-
Activated B-cell	10	27.0	-	-	5	23.8	-	-	15	25.9	-	-
Presentation site												
Chest wall	1	2.7	-	-	0	0.0	-	-	1	1.7	-	-
Naso- oropharynx	7	18.9	-	-	6	28.6	-	-	13	22.4	-	-
Gastrointestinal	3	8.1	-	-	3	14.3	-	-	6	10.3	-	-
Cervical	12	32.4	-	-	8	38.1	-	-	20	34.5	-	-
Inguinal	7	18.9	-	-	2	9.5	-	-	9	15.5	-	-
Axilla	5	13.5	-	-	0	0.0	-	-	5	8.6	-	-
Ophthalmic	1	2.7	-	-	1	4.7	-	-	2	3.5	-	-
Breast mass	0	0.0	-	-	1	4.7	-	-	1	1.7	-	-
Mediastinum	1	2.7	-	-	0	0.0	-	-	1	1.7	-	-
Mortality												
Alive	25	67.6	-	-	12	57.1	-	-	37	63.8	-	-
Dead	12	32.4	-	-	9	42.9	-	-	21	36.2	-	-

IQR, interquartile range; HIV, human immunodeficiency virus; TLD, tenofovir lamivudine dolutegravir; TEE, tenofovir emtricitabine efavirenz; ALD, abacavir lamivudine dolutegravir; EBV, Epstein-Barr virus.

staging was stage IV (53.5%). Post-treatment interval imaging showed a significant shift to earlier stages ($p = 0.042$). Nodal presentation occurred in 60.3% of patients, most frequently at the cervical site (34.5%). Extranodal involvement was seen in 39.7%, with the nasopharyngeal area being the most common site across sexes (Table 1). Double-hit lymphoma was identified in 8.6% of patients, more frequently in females (14.3%) than males (5.4%) (Figure 1).

Rituximab with Cyclophosphamide, hydroxydaunorubicin hydrochloride, oncovin and prednisone was the primary chemotherapy regimen in 74.1% of patients (Table 2). Most received either six or eight cycles (each 37.9%). After first-line therapy, 50.0% achieved complete remission, 43.1% had a partial response and 6.9% were refractory. Among those needing second-line treatment, the most used regimen was again R-CHOP (10.3%), followed by Rituximab Cyclophosphamide Vincristine prednisone (RCVP) (6.9%). In this group, 20.7% achieved complete remission, 5.2% had a partial response and 6.9% remained refractory. One patient received a third-line regimen (R-GemOx) but was refractory (Table 2).

Thirteen patients (22.4%) received intrathecal chemotherapy; five received two or three doses. Seven patients (12.1%) relapsed, with a median time to relapse of 7 months (IQR 6–9). Thirteen patients (22.4%) received radiotherapy, most commonly to the neck (8.6%). No patients underwent stem cell transplant.

Outcomes varied by immune status and treatment response. For a median follow-up of 2 years, of HIV-positive patients, those with CD4 < 200 cells/μL had higher mortality (57.1%) compared to those with CD4 > 200 ($p = 0.022$) (Table 3). Complete remission after initial chemotherapy was associated with survival in 67.6% of cases ($p = 0.001$). Following second-line chemotherapy, complete remission correlated with 24.3% survival, while no patients with refractory disease survived ($p = 0.024$). Relapse occurred in 12.1% of patients and was significantly associated with mortality ($p = 0.004$) (Table 4).

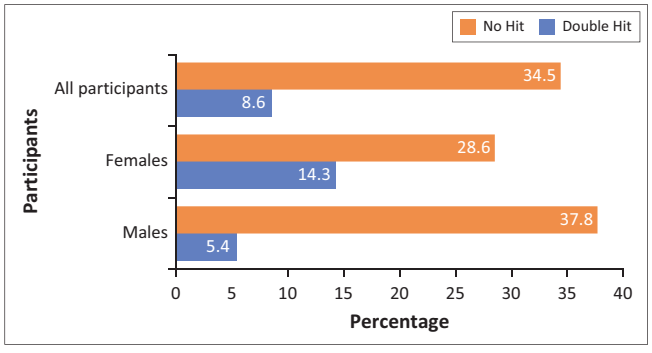


FIGURE 1: A description of the associated MYC, BCL2 and BCL6 fluorescence *in situ* hybridisation findings as either no rearrangement or double hit by sex (there were no triple hits in this cohort).

At last follow-up, 63.8% of patients were alive. One-year overall survival was 78.2% (95% CI 64.8–87.0%), declining to 53.1% (95% CI 36.7–67.0%) by year three (Figure 2). Log-rank analysis revealed no statistical difference between the groups. Survival by sex at year one was slightly higher in men (80.0%) than women (75.0%)

TABLE 2: Treatment received, response to treatment and the percentage of patients that develop refractory or relapsed disease among patients treated for diffuse large B-cell lymphoma by sex.

Characteristic	Male patients		Female patients		Total	
	n = 37 (63.8%)		*n* = 21 (36.2%)		*N* = 58 (100%)	
	n	%	*n*	%	*n*	%
Treatment regimen						
R-CHOP	28	75.7	15	71.4	43	74.1
R-EPOCH	3	8.1	1	4.8	4	6.9
R-CHEP	4	10.8	0	0.0	4	6.9
DA-EPOCH-R	1	2.7	0	0.0	1	1.7
RCVP	1	2.7	0	0.0	1	1.7
CEVP	0	0.0	1	4.8	1	1.7
CHOP	0	0.0	4	19.1	4	6.9
Number of chemotherapy cycles						
1	0	0.0	1	4.8	1	1.7
2	2	5.4	1	4.8	3	5.2
3	0	0.0	1	4.8	1	1.7
4	2	5.4	2	9.5	4	6.9
5	2	5.4	0	0.0	2	3.5
6	14	37.8	8	38.1	22	37.9
7	1	2.7	2	9.5	3	5.2
8	16	42.2	6	28.6	22	37.9
Response to treatment						
Complete remission	19	51.4	10	47.6	29	50.0
Partial response	14	37.8	11	52.4	25	43.1
Refractory	4	10.8	0	0.0	4	6.9
Salvage therapy						
RCHOP	3	8.1	3	14.3	6	10.3
ESHAP	0	0.0	1	4.8	1	1.7
RICE	1	2.7	1	4.8	2	3.5
DHAP	1	2.7	0	0.0	1	1.7
RCVP	3	8.1	1	4.8	4	6.9
RCEOP	1	2.7	0	0.0	1	1.7
RESHAP	2	5.4	0	0.0	1	3.5
Rituximab	0	0.0	1	4.8	1	1.7
Bendamustine, Rituximab	0	0.0	1	4.8	1	1.7
Number of salvage therapies						
1	0	0.0	1	4.8	1	1.7
2	7	18.9	1	4.8	8	13.8
3	1	2.7	2	9.5	3	5.2
4	2	5.4	2	9.5	4	6.9
6	0	0.0	1	4.8	1	1.7
7	1	2.7	0	0.0	1	1.7
8	0	0.0	1	4.8	1	1.7
Response to salvage therapy						
Complete remission	7	18.9	5	23.8	12	20.7
Partial response	2	5.4	1	4.8	3	5.2
Refractory	2	5.4	2	9.5	4	6.9

R-CHOP, rituximab cyclophosphamide hydroxydaunorubicin oncovin prednisone; R-EPOCH, rituximab etoposide prednisone oncovin cyclophosphamide hydroxydaunorubicin; R-CHEP, rituximab cyclophosphamide hydroxydaunorubicin etoposide prednisone; DA-EPOCH-R, dose adjusted rituximab etoposide prednisone oncovin cyclophosphamide hydroxydaunorubicin rituximab; RCVP, rituximab cyclophosphamide vincristine prednisone; CEVP, cyclophosphamide etoposide vincristine prednisone; CHOP, cyclophosphamide hydroxydaunorubicin oncovin prednisone; ESHAP, etoposide cytarabine cisplatin methylprednisolone; RICE, rituximab fractionated ifosfamide carboplatin etoposide; DHAP, dexamethasone high-dose cytarabine cisplatin; RCEOP, rituximab cyclophosphamide etoposide oncovin prednisone; RESHAP, rituximab etoposide cytarabine cisplatin methylprednisolone.

(p value = 0.427), and by year three, it was 58.4% in men versus 43.4% in women (p value = 0.83) (Figure 3). HIV-positive patients had a similar year- one survival (78.3%) compared to HIV-negative patients (77.8%) (p value = 0.965), but by year three, survival dropped to 51.6% in the HIV-positive group compared to 57.0% in HIV-negative individuals (Appendix 1, Figure 1-A1).

Discussion

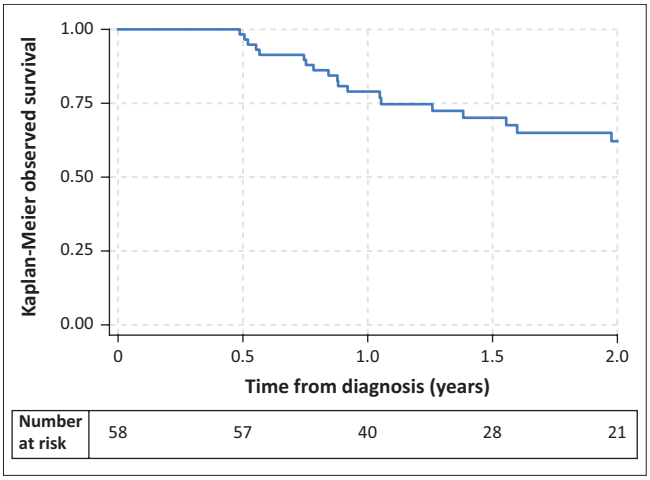
A total of 58 patients were eligible to be included in this study, barring inclusion and exclusion criteria. This study found that most patients were men, 37 (63.8%), as compared to women, 21 (36.2%). Two local studies found a female predominance in their retrospective studies; however, one of the studies only included HIV-negative patients.[11] The other study looked at DLBCL in a low-resource setting; however, it had missing data that could account for the represented demographic.[12] Other studies found a male predominance in their demographic group.[13,14] A study on lymphoproliferative disorders conducted at CMJAH, which had a much larger population group as compared to our study, found a 1:1 male-to-female predominance in the HIV-positive group; however, a 1:4 male-to-female predominance in the HIV-negative group.[15] Even among the HIV-negative patients, our study showed a marginally higher male (24.3%) than female (23.8%) distribution.

The clinic treated more patients of black African descent (77.6%) than any other ethnicity. This likely reflects the community that the hospital serves and is an extension of the local hospitals that refer to this academic centre.[15] The black African population still lives below the poverty margin and has limited access to private healthcare services. There is limited data on ethnicity in this field of research in our context. The median age in the study population was 49; this is younger than what international studies observe, where the median age is 60 years and above.[2,16] The younger

TABLE 3: Clinical data of patients treated for diffuse large B-cell lymphoma by HIV status and patient outcome.

Characteristics	Patient outcome					
	Alive		Dead		Total	
	n = 37 (63.8%)		n = 21 (36.2%)		N = 58 (100%)	
	n	%	n	%	n	%
HIV status						
HIV positive	28	75.7	16	76.2	44	75.9
HIV negative	9	24.3	5	23.8	14	24.1
CD4 count (cells/μL)						
< 200	10	27.0	12	57.1	22	37.9
> 200	15	40.5	2	9.5	17	29.3
HIV viral load (copies/mL)						
< 50	9	24.3	5	23.8	14	24.1
> 50	15	40.5	8	38.1	23	39.7
Outcome by histology type						
Germinal centre	19	51.4	10	47.6	29	50.0
Activated B-cell	13	35.1	2	9.5	15	25.9

HIV, human immunodeficiency virus; CD4, cluster of differentiation four; VL, viral load.



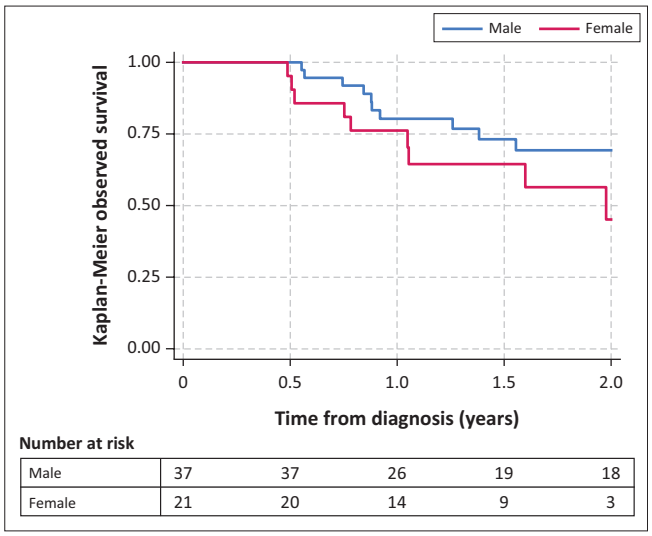
DLBCL, diffuse large B-cell lymphoma.

FIGURE 2: Kaplan–Meier overall observed survival of patients treated for diffuse large B-cell lymphoma at Charlotte Maxeke Johannesburg Academic Hospital from July 2020 to June 2022.

TABLE 4: Treatment received, response to treatment and the percentage of patients that develop refractory or relapsed disease among patients treated for diffuse large B-cell lymphoma at Charlotte Maxeke Johannesburg Academic Hospital from July 2020 to June 2022, by patient outcome.

Characteristic	Patient outcome															p
	Alive					Dead					Total					
	n = 37 (63.8%)					n = 21 (36.2%)					N = 58 (100%)					
	n	%	Median	Q1	Q3	n	%	Median	Q1	Q3	n	%	Median	Q1	Q3	
Response to chemotherapy regimen one																0.001*
Complete remission	25	67.6	-	-	-	4	19.1	-	-	-	29	50.0	-	-	-	
Partial response	11	29.7	-	-	-	14	66.7	-	-	-	25	43.1	-	-	-	
Refractory	1	2.7	-	-	-	3	14.3	-	-	-	4	6.9	-	-	-	
Response to chemotherapy regimen two																0.024*
Complete remission	9	24.3	-	-	-	3	14.3	-	-	-	12	20.7	-	-	-	
Partial response	1	2.7	-	-	-	2	9.5	-	-	-	3	5.2	-	-	-	
Refractory	0	0.0	-	-	-	4	19.1	-	-	-	4	6.9	-	-	-	
Response to the chemotherapy regimen three																
Refractory	0	0.0	-	-	-	1	4.8	-	-	-	1	1.7	-	-	-	0.181
Relapse																0.004*
Yes	1	2.7	-	-	-	6	28.6	-	-	-	7	12.1	-	-	-	
No	36	97.3	-	-	-	15	71.4	-	-	-	51	87.9	-	-	-	
Time to relapse	-	-	12	12	12	-	-	7	6	9	-	-	7	6	9	0.286

Q1, quartile one; Q3, quartile three.
*, statistical significance.



Number at risk

Male	37	37	26	19	18
Female	21	20	14	9	3

DLBCL, diffuse large B-cell lymphoma.

FIGURE 3: Kaplan–Meier observed survival of patients treated for diffuse large B-cell lymphoma at Charlotte Maxeke Johannesburg Academic Hospital from July 2020 to June 2022, stratified by sex.

age at presentation may likely be related to the high HIV prevalence[11,12,1] and low socio-economic infrastructures that, in turn, affect health-seeking behaviour for the marginalised.[11,12,13,17,18] It is also important to note that South Africa had a younger average life expectancy of 64.6 years in 2021,[19] which can also account for this trend in our data. A local study with HIV-negative participants showed a median age of 55,[11] also lower than what is described in international literature, which shows that multiple factors can account for the younger presentation of this lymphoma.

The study exhibited a high HIV-positive population of 75.9%, with the majority of patients on antiretroviral treatment. Of these patients, 37.9% had a CD4 of less than 200 cells/μL, and 39.7% had an unsuppressed viral load of more than 50 copies/mL. As per many studies, this confers a link between a high incidence of HIV and DLBCL.[4,11,15,20,21] This is likely because of supporting evidence that HIV has both a direct and indirect effect on the pathogenesis of DLBCL and that uncontrolled HIV infection and poor immune status are associated with poor outcomes.[5,22] The study demonstrated that patients with a low CD4 < 200 cells/μL had a higher mortality of 57.1% which was statistically significant with a *p*-value of 0.022. This is consistent with a study that showed patients with a low CD4 count, cut off used in said study was CD4 < 150 cells/μL, had reduced survival and were 2.4 times more likely to die in comparison to the HIV-negative group.[5]

The study population did not demonstrate any noted risk factors, with 82.8% of patients having no associated risks other than HIV. The clinic does not routinely test for co-infection with Epstein-Barr virus (EBV), and in this sample, only one individual had a documented test carried out on referral, which was positive. A local study found that EBV occurs in 14% of DLBCL cases,[13] given the low occurrence, which may inform low testing in this clinical setting. The majority of the patients did not have other associated co-morbidities (69%), and this is likely in part related to the younger population in the study, where hypertension, diabetes and complications are not commonly observed. A meta-analysis study suggests a median age of 56.7 years in South Africa.[23]

Our study demonstrated the germinal centre subtype to prevail among male and female groups. A study within our context compared HIV status to the histological cell of origin and found that germinal centres frequently occurred in HIV-positive patients and non-germinal centres in HIV-negative patients.[6] In contrast, another study demonstrated an even distribution of DLBCL subtype among HIV-positive and HIV-negative over a longer period, and that the pathogenesis for germinal and non-germinal centre occurs equally.[5] Our study would more likely be similar to the findings of the former study, as our population sample was predominantly HIV-positive. However, our population sample was much smaller.

Double-hit lymphomas are not common; however, when they do occur, they have a male predominance and are associated with a poor prognosis.[24,25] We exhibited a low occurrence of double-hit lymphoma (8.6%), with a female predominance of 14.3% as compared to 5.4% in male patients. It is important to note that fluorescence *in situ* hybridisation (FISH) is not always performed or available in our setting or from peripheral referral hospitals because of cost constraints or sometimes insufficient samples acquired at biopsy to run the test. This makes the accurate interpretation of data difficult.

Patients more commonly presented with advanced disease, as initially CT/PET demonstrated. The most common stage was stage four (53.5%) at presentation. Following treatment, the most common intervals were the early stage (27.6%) and stage one (25.9%), which were statistically significant with a *p*-value of 0.042. The advanced stage in the presentation likely reflects the burden of HIV-associated lymphoma, as it is known to be associated with extranodal sites and advanced clinical disease.[5] The clinic provides an oncology service to a disadvantaged population with a low socio-economic background; it is thus important to acknowledge that this group of people exhibits delayed health-seeking behaviour, which can contribute to the advanced clinical presentation.[17]

This study demonstrated that nodal disease was still the most common presenting site for lymphoma. The most frequently presenting lymph node sites were cervical lymph nodes in both genders. The clinic commonly received patients with DLBCL diagnosed from the naso-oropharyngeal area as the primary presenting site among the extranodal presentations in both genders. Several data also reflect that primary nodal disease is still the chief presenting site for this lymphoma.[5,12,13] A study found that bone marrow involvement is the most common site of extranodal involvement.[25] At the time of diagnosis and initial presentation,

we did not see this trend. This could be in part because of a CT scan being the initial and readily available imaging modality at presentation, and that the site of bone marrow trephine and aspirate did not demonstrate infiltrated disease.

The clinic uses RCHOP as the first-line chemotherapy in the treatment of DLBCL, with 74.1% of patients receiving this regimen for six or eight cycles (37.9%) each. The clinic does not routinely make use of the International Prognostic Index (IPI) to help guide the treatment course and duration. Chemotherapy is given at the earliest onset from presentation and continued until interval radiological imaging with CT/PET-CT is performed. Awaiting restaging, they are assessed clinically for residual lymphadenopathy and the presence of B-symptoms. The use of RCHOP is globally accepted and utilised in the modern-day treatment of DLBCL.[11,26,27] Following the initial chemotherapy regimen, 50% of patients achieved complete remission, whereas 43.1% had a partial response and 6.9% refractory to treatment. When comparing outcomes according to survival, of the 50% that achieved complete remission, 67.6% were alive at the end of treatment. Of those that had a partial response, 29.7% were alive at the end of treatment, and only 2.7% survived with a refractory response. This was statistically significant, with a *p*-value of 0.001. Rituximab cyclophosphamide hydroxydaunorubicin oncovin prednisone is associated with a higher rate of complete remission as compared to CHOP or CHOP-like regimens.[28] As in a similar study, it is observed that 30% – 50% of the general population treated will achieve complete remission after RCHOP.[29]

The patients who failed to achieve complete remission following initial chemotherapy received a second chemotherapy agent. Of the agents chosen, RCHOP was still the most frequently used regimen (10.3%), followed by RCVP (6.9%), R-ICE (3.5%) and RESHAP (3.5%). The choice of regimen used was clinician-based and with collaboration from patient input and performance status. It is not clear how many of these patients exhibited genetic rearrangement or gene overexpression, which could have played a role in the poor response to initial chemotherapy. In this group of patients, 20.7% achieved complete remission, 5.2% showed a partial response and 6.9% were refractory to treatment. Only one patient received a further new third line of chemotherapy and was still refractory to treatment. The patients who survived following a second chemotherapy regimen and achieved complete remission were 24.3%. Those who showed a partial response and survived were dismal, with only 2.7% surviving. Those refractory to treatment did not survive.

Outcomes following second-line chemotherapy were statistically significant with a *p*-value of 0.024. There were no recipients of stem cell transplants, as there were inadequate resources to perform the procedure. The outcomes of the patients who did not achieve complete remission following initial chemotherapy are not surprising. It is expected that a portion of those patients with DLBCL will not respond to initial chemotherapy.[29] Those that are refractory to treatment or demonstrate early relapse generally have a poor prognosis.[30,31] Patients with primary refractory disease or who show relapse should receive salvage high-dose chemotherapy with or without stem cell transplantation, if eligible for it, to help improve overall survival.[29] Even those that do receive salvage chemotherapy and stem cell transplant as a third-line option still demonstrate poor overall survival of 4.4 months.[32] Ultimately, there are limited options for patients who do not respond to treatment with relatively ominous outcomes. The evolving chimeric antigen receptor T-cell (CAR-T) and bispecific antibodies may change this outlook.

A few patients received intrathecal (IT) chemotherapy, for which the indication was not clearly documented. However, it is presumed that those who received it were at high risk for potential CNS relapse. A study that reviewed CNS IT chemotherapy prophylaxis in HIV-negative patients found that giving IT chemotherapy to a high-risk group can reduce the risk of CNS relapse.[33] However, the effectiveness of IT chemotherapy remains controversial. High-dose methotrexate may be of value in a subset of high-risk patients.[33]

A total of 22.4% of patients received consolidative radiation for residual local disease. Multiple studies infer an overall benefit of up to 15% when radiotherapy is used after RCHOP chemotherapy.[34]

The time to relapse for patients was early, with a median time of 7 months observed in 12.1% of the study population. The published relapse rate with RCHOP is 20% – 30%.[29] The patients that relapsed and demised accounted for 28.6%, statistically significant with a *p*-value of 0.004. Early relapse is notoriously associated with poor outcomes, as exhibited in our study and other studies.[30,31]

The overall survival at year one was 78.2% and by year three, 53.1%. Given the low resource setting of our study in a developing country, the results depicted are encouraging. A local retrospective study that only included HIV-negative patients showed an overall survival of 77% by year three.[11] This highlights the significant impact that HIV status has on disease presentation and overall outcome.

Limitations

An electronic database system is needed to capture information and allow for more efficient retrieval. The clinic underutilises IPI to help risk-stratify patients and plan for treatment. Because of resource limitations, there is insufficient use of high-dose salvage chemotherapy with autologous stem cell transplant (ASCT). Early detection and referral to the central hospital can reduce the number of advanced cases presented. The study sample was limited to a small number of patients, which restricted the study's statistical power and its ability to yield statistically significant results. Additionally, the study was non-randomised and retrospective, with a

major limitation being the lack of available records. To address this limitation, the internal validity of the results is supported by the uniformity, accuracy, and consecutive nature of the data collection.

Conclusion

This study found that DLBCL occurs in a younger population than previously described in the international literature. The burden of HIV significantly influences the pathogenesis, clinical presentation and overall outcomes for patients with DLBCL. Rituximab with Cyclophosphamide, hydroxydaunorubicin hydrochloride, oncovin and prednisone was the most commonly used treatment regimen in our setting. However, greater emphasis should be placed on early detection and timely presentation, as well as on salvage chemotherapy with ASCT for refractory or relapsed disease, to improve outcomes. Further studies are needed to understand the pathophysiology of DLBCL in our population and to clarify the factors contributing to treatment outcomes.

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Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

Authors' contributions

T.T. had full access to all the data in the study and takes responsibility for the integrity and accuracy of the data analysis. T.T. drafted the manuscript, while supervisors D.T. and J.M. provided relevant feedback and oversaw the findings of this work. All authors, T.T., D.T. and J.M., contributed to the article, discussed the results, and approved the final version for submission and publication.

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Data availability

The data that support the findings of this study are available on request from the corresponding author, T.T. The data are not publicly available due to patient confidentiality.

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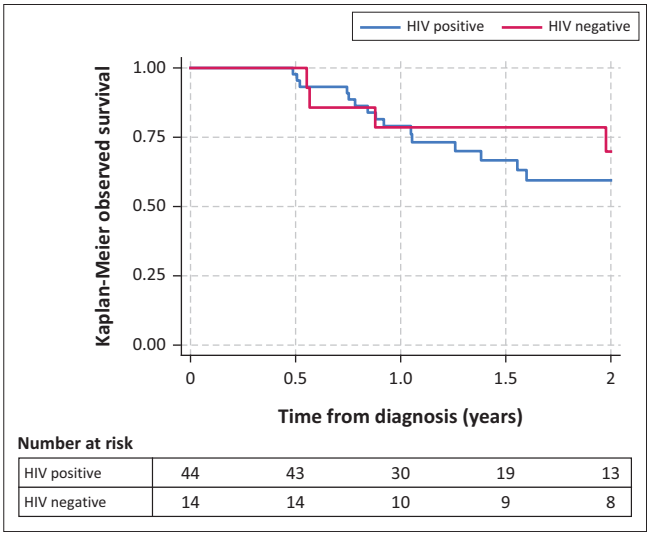
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Appendix 1



Number at risk

HIV positive	44	43	30	19	13
HIV negative	14	14	10	9	8

FIGURE 1-A1: Kaplan–Meier observed survival of patients treated for diffuse large B-cell lymphoma at Charlotte Maxeke Johannesburg Academic Hospital from July 2020 to June 2022, stratified by HIV status.