Evaluation of prognostic risk factors at diagnosis and treatment outcomes in adult patients with early-stage Hodgkin lymphoma in Cape Town, South Africa

Master of Medicine (MMed)

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Declaration

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Format

This is a publication-ready manuscript formatted according to the guidelines of Leukaemia & Lymphoma journal.

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List of Abbreviations

HL	Hodgkin lymphoma
cHL	Classic HL
HIV	Human immunodeficiency virus
EORTC	European Organisation for Research and Treatment of Cancer
GHSG	German Hodgkin Study Group
NCCN	National Comprehensive Cancer Network
ESR	Erythrocyte sedimentation rate
PFS	Progression-free survival
OS	Overall survival
GSH	Groote Schuur Hospital
NHLS	National Health Laboratory Service
NSHL	Nodular sclerosis
MCHL	Mixed cellularity
LRHL	Lymphocyte rich
LDHL	Lymphocyte depleted
CT	Computed tomography
PET CT	Positron emission tomography combined with computed tomography
MMR	Mediastinal mass ratio
ESMO	European Society for Medical Oncology
ABVD	Adriamycin, Bleomycin, Vinblastine, Dacarbazine
DS	Deauville score
ISRT	Involved site radiotherapy
VMAT	Volumetric Arc Therapy
MDT	Multidisciplinary team
ART	Antiretroviral therapy
EBVD	Epirubicin, bleomycin, vinblastine, dacarbazine
AVD	Adriamycin, vinblastine, dacarbazine
ChIVPP	Chlorambucil, vinblastine, procarbazine, prednisolone
R-CHOP	Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone
PLHIV	People living with HIV

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Publication-ready manuscript

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Keywords:

Hodgkin's Lymphoma, prognostic factors, outcomes, early-stage, NCCN guidelines

Abstract

The National Comprehensive Cancer Network (NCCN) Guidelines are a recognized standard for prognostic staging in Hodgkin Lymphoma (HL). We aimed to determine if the NCCN staging system and its individual risk factors correlated with patient treatment outcomes in early-stage adult classical HL (cHL) patients. This retrospective study included 70 patients diagnosed with and treated for early-stage (stage I and II) cHL from 2010 to 2022, at Groote Schuur Hospital Radiation Oncology and Clinical Haematology Units. NCCN unfavourable risk factors assessed were mediastinal mass ratio, presence of bulky disease, B-symptoms, number of nodal regions involved and erythrocyte sedimentation rate. Patients were divided into early-stage favourable (no unfavourable factors) and early-stage unfavourable (any unfavourable factors). Kaplan-Meier curves and log-rank tests were used to compare treatment outcomes between groups.

The median age at diagnosis was 35 years and 50% of the patients were male. Most patients had stage II disease (86%) and were classified as unfavourable (76%). During the study period, 6 patients died (9%) all of whom had stage II unfavourable disease. The 5-year overall survival for the favorable and unfavourable groups was similar (94% vs. 90%, *P*=0.599). Progression free survival at 5 years was also similar (83% vs. 88%, *P*=0.984). This study demonstrates excellent 5-year survival outcomes in early-stage cHL patients.
These findings are comparable with those in higher income countries and were not affected by HIV status or unfavourable risk factors. This highlights the importance of early diagnosis and treatment while patients still have early-stage disease.

Introduction

Hodgkin lymphoma (HL) is a unique neoplasm characterized by large cancerous mononuclear cells derived from the B cell lymphocyte lineage, in an inflammatory background [1]. HL has an incidence of 2–3 per 100,000 individuals per year, however in people living with HIV, the risk of developing HL is significantly increased [2, 3]. HL is largely diagnosed among individuals 15-30 years of age with a second peak around 60 years of age. Classic HL (cHL) accounts for 95% of all HL cases [2].

When treated with first-line combination chemotherapy and radiotherapy, cHL is highly curable. Patients with early-stage cHL (stage I and II) have an especially favourable cure rate exceeding 90-95% [4-9]. However, only a small proportion of patients in South Africa present with early-stage disease. In the human immunodeficiency virus (HIV) and Tuberculosis endemic setting of South Africa, the overlapping symptomatology of these diseases with lymphoma leads to late presentation of patients, and therefore delays in the diagnosis of HL. In a local study, this delay (termed the 'healthcare practitioner interval') was more marked in patients with HL and those on empiric Tuberculosis treatment as well as those patients with advanced disease, highlighting the fact that the longer the time to diagnosis, the more likely the patient is to have developed advanced disease [10]. This results in many patients presenting or being referred for treatment of HL who already have advanced disease. In our setting this is subsequently associated with poor outcomes [10-12]. We observe that HIV positivity additionally confers a worse prognosis in our patients with advanced cHL, in that the five-year OS is 53% in cHL patients with HIV, as opposed to 76% in their HIV negative counterparts [10]. Similarly, a study in the Western Cape indicated that bone marrow infiltration (conferring stage IV disease) and HIV positivity made statistically significant contributions to five-year overall survival [11].

Patients with early-stage cHL can be divided into favourable and unfavourable risk groups, using prognostic staging systems. These are derived from clinical trials in large cooperative groups, namely the European Organization for Research and Treatment of Cancer (EORTC), German Hodgkin Study Group (GHSG), and the National Comprehensive Cancer Network (NCCN) [13-15]. The common risk factors considered by these groups include age, mediastinal adenopathy, number of involved nodal regions, B-symptoms, erythrocyte sedimentation rate (ESR), bulky disease and extra nodal lesions [14]. More specifically, the four risk factors in the NCCN staging system are: (1) mediastinal adenopathy, (2) involvement of >3 nodal regions, (3) B-symptoms or ESR ≥50 mm/hr and (4) bulky disease [16]. This is the risk stratification used in our setting which provides a standardized approach to the diagnosis, treatment, and follow-up of lymphoma. Previous studies have investigated the impact of NCCN risk groups on patient outcomes with mixed results. Some found that early-stage favourable patients had a higher overall survival compared to early-stage unfavourable patients, while others found no difference [5, 17, 18]. Although these prognostic staging systems have been validated in large groups, this is not always evident in single centre studies.

In the South African setting, where diagnosis is frequently delayed, our focus was on treatment outcome in patients with early-stage cHL [19]. Data on early-stage outcomes of this patient group overall and by prognostic risk groups in South Africa is limited. The aim of this retrospective study was to determine progression-free survival (PFS) and overall survival (OS) in our early-stage patient cohort and how this correlates with the NCCN staging system and its individual risk factors.

Materials and methods

Study design and participant selection

GSH (Groote Schuur Hospital) is a 970-bed tertiary academic treatment centre, located in the Western Cape Province of South Africa and affiliated with the University of Cape Town. This was a retrospective analysis of patients with early-stage cHL, consecutively treated at the GSH Radiation Oncology and Clinical Haematology Units (patients >13 years of age). Patients were diagnosed from 1 January 2010 to 31 December 2022, and follow-up concluded on 30 November 2023. Patients with cHL were consecutively entered into our REDCap lymphoma patient registry (HREC R024/2018) and early-stage cHL were selected for inclusion in the study [20, 21]. Nodular lymphocyte predominant HL was an exclusion criterion. This study was approved by the Human Research Ethics Committee of the University of Cape Town (HREC 659/2022) and GSH. A retrospective waiver of informed consent was granted for patients included in the lymphoma patient registry before 2018. Written informed consent was obtained for patients included from 2018 onwards.

Demographic and clinical data

Patient data were captured in the REDCap lymphoma patient registry drawing from hospital folders, the National Health Laboratory Service (NHLS), and the Western Cape Hospitals' repositories for imaging data (IntelliSpaceVR PACS Enterprise and NUcMEDVR systems).

Demographics: Patient sex, age, and HIV status at cHL diagnosis were recorded.

Diagnosis: Date of cHL diagnosis corresponded to date of tissue diagnosis. Lymph node specimens were histologically subtyped into nodular sclerosis (NSHL), mixed cellularity (MCHL), lymphocyte rich (LRHL), lymphocyte depleted (LDHL), and HL unspecified according to the revised 2016 WHO Classification [2].

Laboratory results: Laboratory parameters assessed were haemoglobin, albumin, white cell count, lymphocyte count and ESR. Blood results at diagnosis or within 2 weeks of diagnosis were studied.

Staging: Imaging for staging at baseline included computed tomography (CT), or [18F]-fluoro-deoxy-glucose positron emission tomography combined with computed tomography (PET-CT). The majority of patients had a baseline PET-CT, but due to logistical and resource constraints, some patients were staged with CT. Patients with modified Lugano stage I and II, classified as early-stage cHL were included [22].

Prognostication: Patients were classified according to the NCCN scoring system into early-stage favourable (stage I–II with no unfavourable factors) and early-stage unfavourable (stage I–II with any of the unfavourable factors, which includes a mediastinal mass ratio (MMR) >0.33, more than three involved nodal regions, B symptoms or ESR ≥50 mm/hr, and bulky disease) [13]. MMR is the ratio of the maximum width of the mass and the maximum intrathoracic diameter seen on chest x-ray. Bulky disease is defined as any single node or nodal mass >10cm in diameter.

Treatment: Patients were treated based on the NCCN and The European Society for Medical Oncology (ESMO) Guidelines but adapted according to local resource constraints. Patients received two cycles of ABVD (Adriamycin, **b**leomycin**, v**inblastine**, d**acarbazine), followed by PET-CT and risk-adapted treatment. During the study period 2010 to 2022 NCCN guidelines were regularly updated and ESMO guidelines were published in 2014 and 2018 [5]. Our local guidelines evolved based on the international standard of care, but the main adaptation necessitated due to local resource constraints was that escalated BEACOPP was not included in our protocol for patients with ESMO limited and intermediate stage cHL (NCCN stage 1 and 2 favourable and unfavourable) who had PET-positive disease after 2 cycles of ABVD. The definition of PET-positive in our protocol was Deauville ≥3 as used in HD10, H10

and UK RAPID trials. Indications for radiotherapy were according to ILROG (International Lymphoma Radiation Oncology Group), ESMO and NCCN guidelines[16]. Stage 1 and 2 patients were managed with combined modality or a chemotherapy-only approach. Very good risk disease according to the GHSG would get 2 cycles of ABVD and 20Gy involved site RT. The ESMO intermediate stage (or NCCN poor risk early stage) would get 4 cycles of ABVD and 30.6Gy ISRT.

Response assessment: Response assessment was based on the International Working Group criteria and incorporated regular updates from the NCCN guidelines into our clinical treatment regimens [13, 22]. Early interim PET-CT after two cycles of ABVD was used to assess response and guide further clinical management. Patients with a Deauville score (DS) of 1 to 3 completed three cycles of ABVD if they were assessed as having favourable disease or four cycles of ABVD if they had unfavourable disease. Both groups received 30Gy involved site radiotherapy (ISRT). Patients were treated with an ABVD-only regimen if they chose not to have radiotherapy, if there were any contraindications to radiotherapy or too many sites of disease to safely deliver radiotherapy, and if pre- chemotherapy imaging was inadequate. Prior to 2012, ISRT was delivered using 3D conformal radiotherapy, but since 2012 all patients are treated with Volumetric Arc Therapy (VMAT). Patients with a DS of 4 with focal positivity were treated with ISRT to 36Gy after completing four cycles of ABVD. This was followed by an end of treatment PET-CT. Those with DS 4-5 at interim PET-CT with suspicion for refractory disease were discussed at a multidisciplinary team (MDT) meeting involving radiation oncology and clinical haematology and referred for a biopsy if indicated and offered high dose salvage chemotherapy and ASCT as per protocol.

Statistical Analyses

Data were analyzed using STATA version 18.0 (Stata Corporation, College Station, Texas, USA). Categorical variables were described by frequencies (%) and numerical variables were described by medians (IQR: interquartile range) as data were non-parametric. Overall

survival (OS) and progression-free survival (PFS) were estimated by Kaplan-Meier curves and differences between NCCN groups were tested by the log-rank test. OS was defined as the time from diagnosis to death from any cause, or last encounter (censored) at a public health facility in the Western Cape. PFS was defined as the time from diagnosis to disease progression, relapse, or last encounter. Univariable logistic regression models were used to assess associations between covariates and HL failure (defined as disease progression, refractory disease, or relapse). For all analyses a P value <0.05 was considered statistically significant.

Results

Study population

Patients with early-stage disease were selected from the total cHL population of 387 patients followed-up and treated during the study period, resulting in 70 (18%) early-stage cHL and 317 (82%) advanced stage cHL. The 70 early-stage patients had a median follow-up duration of 4.1 years (IQR: 1.7-6.6 years). Thirty-five (50%) patients were male, and 35 (50%) were female. Median patient age was 35.4 years (IQR: 26.3-44.7; range: 15-63). Most patients were HIV negative (73%), and of the 19 patients (27%) who were HIV positive, 13 (68%) were on antiretroviral therapy (ART) at diagnosis. Table 1 summarizes baseline demographic and clinical characteristics of the 70 included patients.

Prognostication

NCCN scoring system variables are presented in Table 1. An MMR >0.33 was seen in seven patients (10%), bulky disease in ten patients (14%), ESR ≥50 mm/hr in 19 patients (27%), B-symptoms in 27 patients (39%), and involvement of more than three nodal regions in 28 patients (40%). At the time of diagnosis, ten patients (14%) had stage I disease, and 60 (86%) had stage II disease. Of the ten stage I patients, four were classified as NCCN favourable and

six as NCCN unfavourable. Of the 60 stage II patients, 13 were classified as NCCN favourable and 47 as NCCN unfavourable. Figure 2 represents the distribution of patients according to NCCN classification and clinical stage. Overall, the majority of patients (76%) were classified as NCCN unfavourable early-stage HL, and 24% had favourable disease. Fewer patients with HIV were noted to have stage II disease, an MMR >0.33, more than three nodal regions involved and unfavourable disease while more had an ESR ≥50 mm/hr when compared with the HIV negative patients in this study.

Treatment

Treatment modalities used are displayed in Table 2. As primary treatment, 36 patients (51%) received chemotherapy and ISRT, while 34 patients (49%) received chemotherapy alone. The most common chemotherapy regimen used was ABVD (in 93% of patients). Other chemotherapy regimens included 6 cycles of EBVD (epirubicin, bleomycin, vinblastine, dacarbazine) and 3 cycles of AVD (adriamycin, vinblastine, dacarbazine), received by one patient each. One patient received 5 cycles of ChIVPP (chlorambucil, vinblastine, procarbazine, prednisolone), and another patient received one cycle of EBVD and then three cycles of ChIVPP. Finally, one patient received three cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) followed by three cycles of ABVD on histology review. Reasons for the use of ChlVPP were severely reduced left ventricular ejection fraction and inability to tolerate anthracycline chemotherapy. The supply of Doxorubicin was limited at certain times due to logistical supply issues and Epirubicin was substituted. Bleomycin was omitted in a patient with pre-existing lung function abnormalities.

All HIV positive patients not on ART at diagnosis were initiated on treatment prior to receiving chemotherapy and were managed using the same treatment protocols as the HIV negative group.

Imaging to assess response to treatment: Almost all patients were imaged using PET-CT at interim/end of treatment (93%). Three patients had CT restaging, and one patient did not need another scan because the staging PET-CT did not demonstrate evidence of active lymphoma after excision biopsy of the involved lymph node. Four patients did not have an interim or end of treatment scan. Two of these patients were fully treated but were lost to follow up or missed their appointments for CT scans. The other two deviated from their treatment plans as follows: a 20-year-old HIV negative male (stage II unfavourable) and a 28-year-old female with HIV (stage I unfavourable) were planned for four cycles of ABVD and ISRT, but both patients only received two cycles of ABVD. These four patients were classified as having an unconfirmed complete response to treatment and were recorded to be alive at five and 12.5, and eight and 10.5 years after diagnosis, respectively.

End of treatment response assessment: A complete response to primary treatment was documented in 86% of patients, while two patients (3%) had a partial response and four patients (6%) had progressive disease. One patient with a partial response to primary treatment was classified as being refractory on end of treatment PET-CT. The second patient with a partial response on interim scan was lost to follow-up after completing treatment. Lastly, one 25-year-old female with unfavourable disease abandoned therapy after two cycles of ABVD and when salvaged eight months later was lost to follow up again. During the study period, three patients (4%) relapsed after primary treatment. Characteristics of patients who relapsed and patients who had progressive or refractory disease are compared to those without disease progression in Table 3. Of note, all three patients who relapsed were male, HIV negative and had NSHL. The five patients who had progressive or refractory disease were all HIV negative and had stage II NSHL. Similar proportions of patients classified as NCCN favourable and unfavourable were observed across the three response groups.

Outcome and additional associations with overall survival

The data was evaluated for five-year OS according to HIV status and NCCN classification (Figure 3A and 3B). The five-year survival for the total cohort was 91% (95% CI: 78.8-96.2). The five-year survival for the HIV positive and negative groups was 94% (95% CI: 66.6-99.2) and 90% (95% CI: 74.9-96.2, *P*=0.684), respectively. The five-year survival for the favourable group was 94% (95% CI: 65.0-99.2) and that of the unfavourable group was 90% (95% CI: 74.1-96.1, *P*=0.599). PFS curves are shown in Figure 3C and 3D. PFS at five years for the total cohort was 87% (95% CI: 74.9-93.2), while PFS at five years for the HIV positive and negative groups was 100% and 82% (95% CI: 67.2-90.8, *P*=0.86), respectively. PFS at five years for the favourable and unfavourable groups was 84% (95% CI: 46.5-95.9), and 87% respectively (95% CI: 74.0-94.2, P=0.984). At the end of the study 91% of the patients were alive, and six patients (9%) had died. Of note, only two patients (3%) died from progressive disease, all others demised due to unrelated causes. Refer to Table 2 for patient responses and outcomes. In univariable logistic regression no factors were associated with HL failure (disease progression/refractory disease/relapse) (Supplementary Table 1).

Table 1: Baseline demographic and clinical characteristics of the 70 early-stage cHL patients.

	N (%) or Median (IQR)		
Variable	**Total** (N=70)	**HIV Negative** (N=51, 73%)	**HIV Positive** (N=19, 27%)
Sex			
Male	35 (50)	27 (52)	8 (42)
Female	35 (50)	24 (47)	11 (58)
Age (years)	35 (26-45)	34 (26-45)	37 (28-48)
Clinical stage			
I	10 (14)	5 (10)	5 (26)
II	60 (86)	46 (90)	14 (74)
Histological classification			
NSHL	41 (59)	34 (67)	7 (37)
MCHL	15 (21)	8 (16)	7 (37)
LRHL	1 (1)	1 (2)	0
LDHL	2 (3)	0	2 (11)
HL unspecified	11 (16)	8 (16)	3 (16)
Laboratory parameters			
Haemoglobin (g/dL)	12 (10-14)	12 (12-14)	11 (10-14)
Albumin (g/dL) (n=50)	40 (38-44)	41.0 (38-44)	40 (37-43)
Lymphocyte count ($x10^9$/L) (n=67)	2 (1-3)	2.1 (2-3)	2 (1-2)
White cell count ($x10^9$/L)	8 (6-11)	9.1 (7-13)	6 (5-8)
NCCN risk factors			
MMR ratio >0.33			
Yes	7 (10)	7 (14)	0
No	63 (90)	44 (86)	19 (100)
Bulky disease			
Yes	10 (14)	8 (16)	2 (11)
No	60 (86)	43 (84)	17 (90)
ESR ≥50 mm/hr			
Yes	19 (27)	12 (24)	7 (37)
No	23 (33)	17 (33)	6 (31)
Unknown	28 (40)	22 (43)	6 (31)
B-symptoms present			
Yes	27 (39)	22 (43)	5 (26)
No	43 (61)	29 (57)	14 (74)
>3 nodal regions involved			
Yes	28 (40)	24 (47)	4 (21)
No	42 (60)	27 (53)	15 (79)
NCCN classification			
Favourable	17 (24)	10 (20)	7 (37)
Unfavourable	53 (76)	41 (80)	12 (63)

HL: Hodgkin lymphoma; NSHL: nodular sclerosing HL; MCHL: mixed cellularity HL; LRHL: lymphocyte rich HL; LDHL: lymphocyte depleted HL; NCCN: National Comprehensive Cancer Network; IQR: Interquartile range; SD: standard deviation, MMR: mediastinal mass ratio, ESR: erythrocyte sedimentation rate.

Table 2: Treatment methods, patient responses and outcomes.

	N (%)		
Variable	**Total** (N=70)	**HIV-** (N=51, 73%)	**HIV+** (N=19, 27%)
Primary treatment			
Chemotherapy	34 (49)	22 (43)	10 (53)
Combined modality chemotherapy & radiotherapy	36 (51)	29 (57)	9 (48)
First-line chemotherapy regimen			
ABVD	65 (93)	48 (94)	17 (90)
Other*	5 (7)	3 (6)	2 (11)
Response to primary treatment			
Complete response	60 (86)	45 (88)	15 (79)
Partial response	2 (3)	1 (2)	1 (5)
Progressive disease	4 (6)	4 (8)	0
Unconfirmed complete response	4 (6)	1 (2)	3 (16)
Relapse after primary treatment	3 (4)	3 (6)	0
Outcome			
Alive	64 (91)	46 (90)	18 (95)
Died	6 (9)	5 (10)	1 (5)
Cause of death			
Progressive disease	2 (3)	2 (4)	0
Early treatment interruption and refusal	1 (1)	1 (2)	0
Covid pneumonia 3 months post CR	2 (3)	1 (2)	1 (5)
Fatal car accident 8 years post CR	1 (1)	1 (2)	0

*Other chemotherapy includes: 1 EBVD (epirubicin, bleomycin, vinblastine, dacarbazine), 1 AVD (Adriamycin, vinblastine, dacarbazine), 1 ChIVPP (chlorambucil, vinblastine, procarbazine, prednisolone), 1 ChIVPP and EBVD, 1 R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) and ABVD (Adriamycin, bleomycin, vinblastine, dacarbazine).

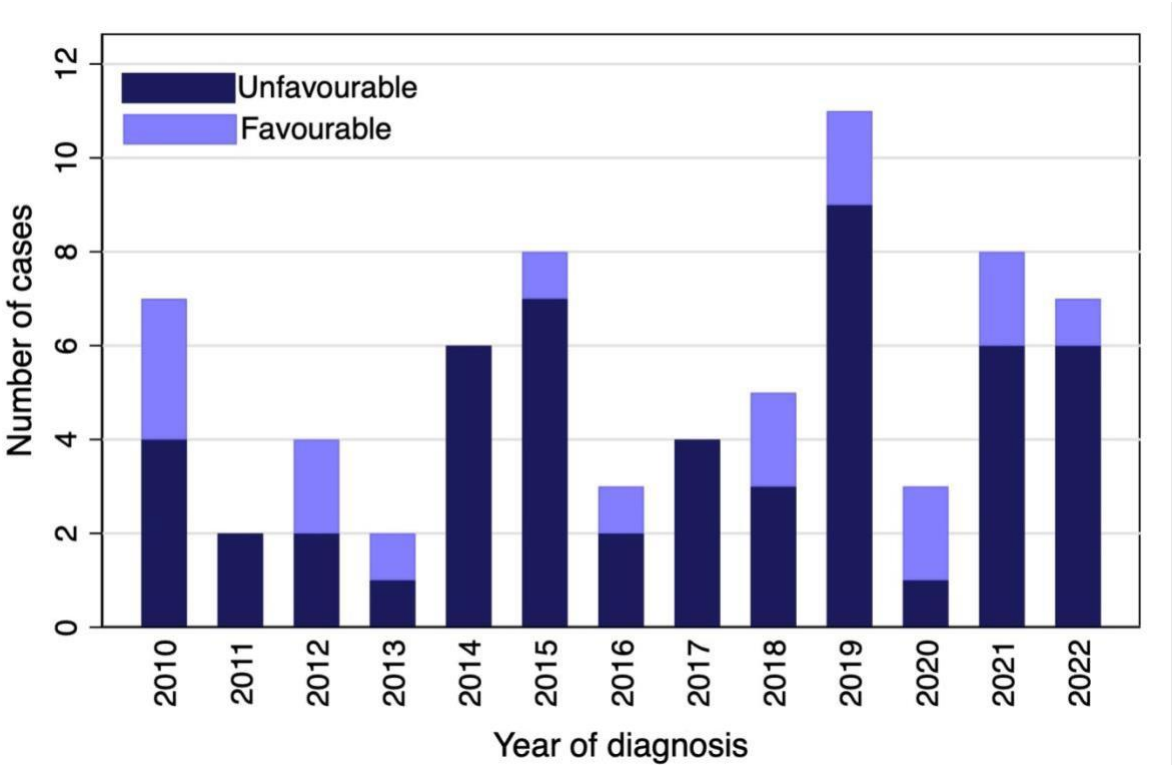

Figure 1: Number of patients diagnosed per year by NCCN classification (favourable and unfavourable).

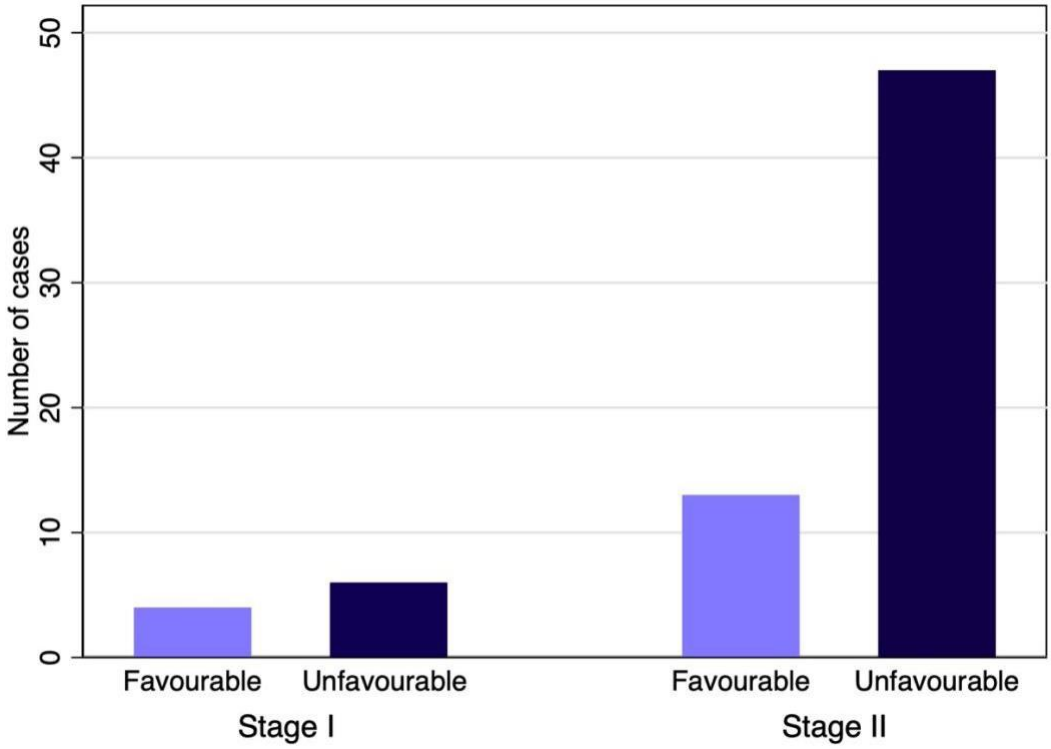

Figure 2: Distribution of patients according to clinical stage and NCCN classification (favourable and unfavourable).

Table 3: Demographic and clinical characteristics by disease status.

	N (%), Median (IQR) or Mean (SD)		
Variable	**Patients without disease progression (N=62)**	**Patients with progressive or refractory disease (N=5)**	**Patients who relapsed (N=3)**
Sex			
Male	29 (47)	3 (60)	3 (100)
Female	33 (53)	2 (40)	0
Age (years)	36 (26-46)	32 (26-33)	35 (21-47)
Age > 50 years	10 (14)	0	0
Clinical stage			
I	9 (15)	0	1 (33)
II	53 (86)	5 (100)	2 (67)
Histological classification			
NSHL	33 (53)	5 (100)	3 (100)
MCHL	15 (24)	0	0
LRHL	1 (2)	0	0
LDHL	2 (3)	0	0
HL unspecified	11 (18)	0	0
HIV status			
Negative	43 (70)	5 (100)	3 (100)
Positive	19 (31)	0	0
NCCN risk factors			
MMR >0.33	5 (8)	2 (40)	0
Bulky disease	8 (13)	2 (40)	0
ESR ≥50 mm/hr	18 (29)	0	1 (33)
B-symptoms present	22 (36)	3 (60)	2 (67)
>3 nodal regions involved	24 (39)	3 (60)	1 (33)
NCCN classification			
Favourable	15 (24)	1 (20)	1 (33)
Unfavourable	47 (76)	4 (80)	2 (67)

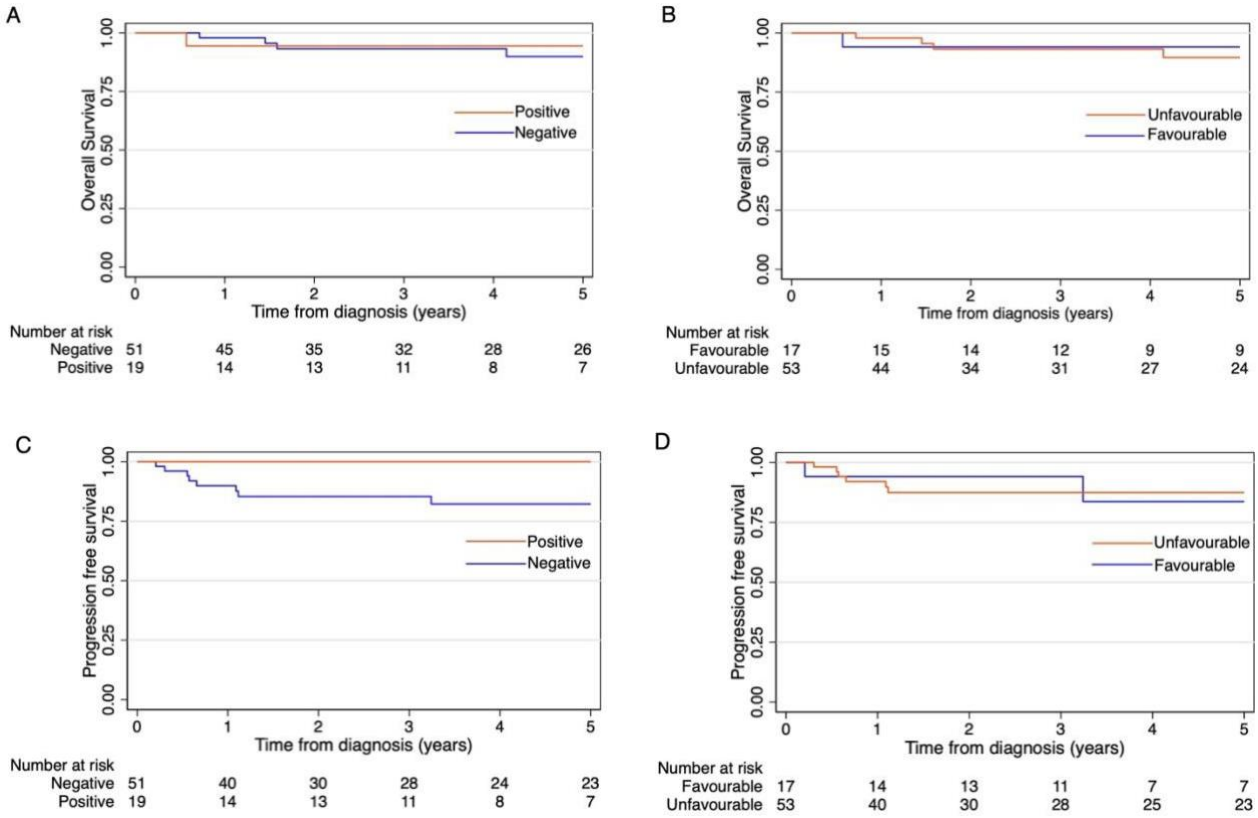

Figure 3: Kaplan–Meier Curves of five-year overall survival by (A) HIV status (P=0.684) and (B) NCCN classification (P=0.599). Progression-free survival by (C) HIV status (P=0.086) and (D) NCCN classification (P=0.984).

Discussion

This retrospective analysis of adults with early-stage cHL showed excellent patient outcomes with a 91% five-year OS. This is in alignment with outcomes from single centre and multicenter studies as well as national cancer registries around the world, reporting four-to-five-year OS for early-stage cHL patients ranging from 76-100% [7, 17, 24-26]. In this small cohort of 70 patients, we could not show a notable difference in outcome according to HIV status or NCCN risk stratification. We found similar five-year OS of 94% and 90% for the favourable and unfavourable NCCN risk groups, respectively. In other studies, from the

sub-Saharan African region, risk stratification was not applied in early-stage cHL cohorts [7, 11, 24]. In small single-centre reports that applied risk stratification, significant contrasts between the favorable and unfavorable cohorts were inconsistently demonstrated [4, 17]. This contrasts with the significantly different outcomes reported when risk stratification was applied in the large cooperative groups from which these parameters were derived [5].

Our results indicate a complete response to treatment in 86% of early-stage cHL patients, only 7% of patients had refractory disease and 4% of patients relapsed after primary treatment, all of whom were HIV negative. An unexpected observation is that patients living with HIV exhibited outcomes at least as favourable as the patients without HIV. HIV positivity bore no significant influence on the likelihood of relapse or refractory status. It is pertinent to note that all instances of disease progression were observed exclusively among HIV negative patients.

Another overlapping study conducted in our institution by K. Simba et al included 285 patients diagnosed with and treated for cHL from 2010 to 2019, and 75% of the early-stage cHL patients were identified as HIV negative [19]. This correlation aligns with findings from a study conducted in France, where no difference in outcomes for cHL between HIV positive and HIV negative patients was detected [27]. However, a third study performed in our institution by K. Antel in 2019 demonstrates contrasting outcomes in the context of people living with HIV (PLHIV). Specifically, the five-year OS for cHL in PLHIV was reported at a modest 53% [12]. It is noteworthy that this disparity might be attributed, at least in part, to the advanced HIV disease stage within this cohort, and these patients were less likely to be on antiretroviral therapy [12].

Early-stage cHL constitutes only a small proportion of the total number of patients with cHL in this study at 18% (70 of 387 patients). The outcomes seen in our early-stage cHL cohort

are not dissimilar to the outcomes seen in community-based and multicenter studies in the developed world. In contrast, the outcomes from our centre in advanced stage patients show that the association of HIV and advanced stage prognostic variables confer notably worse outcomes than those seen in large centre studies from high income countries [5,11,19]. This has also been found in small centre cohorts of predominantly advanced stage patients with poor outcomes and has been reported in paediatric cHL in South Africa as well as in Ethiopia [4,24]. We have shown that delayed diagnosis due to poor access to accurate diagnostic techniques leads to a larger proportion of advanced stage patients with poor prognosis [10]. In our setting, prolonged intervals between symptom onset and diagnosis are recurrent, and this is even more pronounced in PLHIV. This delay is often attributed to the initiation of empiric Tuberculosis therapy due to the diagnostic challenges in differentiating Tuberculosis, HIV and other opportunistic infections and inadvertently obscures the underlying pathology [10].

This study has several limitations, mainly as a result of its retrospective design. This format is restricted both by the scope and availability of patient and laboratory data (including ESR, crucial for prognostic assessment), particularly among individuals diagnosed prior to 2015. Secondly, the study's sample size is small, nevertheless this should be seen in the context of the much larger total cHL cohort. Furthermore, the retrospective acquisition of CT and PET-CT reports introduced a potential source of variability, as the assurance of standardized reporting could not be guaranteed uniformly across the dataset. Moreover, no multivariate analyses were conducted due to the small number of events.

Conclusion

This study serves to highlight the risk determinants and outcomes of a small population of patients that have not yet been described in Africa. Early-stage cHL has excellent outcomes, but unfortunately in our setting this represents the minority of patients presenting with this

disease, due to various patient and healthcare-related factors. Despite this, and the other limitations experienced in our resource constrained setting, these early-stage cHL patients had five-year overall and progression free survival rates comparable with those in higher income countries. This is true for both patients living with HIV in this era of safe, effective, accessible ART, as well as for those with unfavourable disease. In the broader context of managing patients with cHL, here we clearly present the urgent need to identify and diagnose these patients early. This will shift the high proportion of patients with advanced disease and subsequent poor outcomes currently seen to a picture where the burden of disease consists more of early-stage disease with the excellent outcomes described here. Similarly, meticulous disease staging, and the identification of adverse prognostic factors are of importance in developing tailored therapeutic plans for our patients, potentially amplifying the ability to achieve remission while simultaneously minimizing treatment-related toxicity, however more research is needed in this regard.

Supplementary Table 1: Univariable logistic regression analyses of factors associated with HL failure (disease progression/refractory disease/relapse)

Variable	Odds ratio	95% CI	P-value
Age	0.96	0.89-1.02	0.204
Age >50*	-	-	-
HIV status**	-	-	-
Clinical stage II	1.19	0.13-10.85	0.878
NCCN unfavourable	0.96	0.17-5.25	0.960
MMR >0.33	3.80	0.60-24.00	0.156
Bulky disease	2.25	0.39-13.13	0.368
ESR	1.00	0.97-1.04	0.834
ESR ≥50 mm/hr	1.22	0.07-20.94	0.890
B symptoms	3.03	0.66-13.90	0.154
> 3 nodal regions	1.58	0.36-6.94	0.542

*all patients who progressed were younger than 50
** all patients who progressed were HIV negative

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Disclosure statement

The authors report there are no competing interests to declare

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None

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Appendices

Appendix A: Haematology Patient Registry Consent Form

Haematology Department, Groote Schuur Hospital
Main Road, Observatory, 7925

Consent for patient information to be collected in the E5 Clinic Haematology Database

What is the E5 Clinic Haematology database and what is it used for?

- The E5 Clinic Haematology database collects medical information from all patients with blood diseases in our clinic (E5 Clinic, E Floor, New Main Building, Groote Schuur Hospital, Observatory, Cape Town, 7925).
- This information is used to improve the service and the care delivered to you
- This database will record routine clinical data electronically rather than on paper to prevent information from being lost.
- The information is important for healthcare planning. It allows treaters and patients to negotiate and lobby with government and other care providers to improve services.
- We will collect information on demographics, medical history, diagnosis and treatment.

Will information about you be used for research?

Information from the database may be used to study haematological disorders, however ethical approval will be sought from the local ethics committee for this new research and all reports will use de-identified information to maintain your privacy.

How will your privacy and confidentiality be protected?

- The National Health Act of 2003 stipulates that medical records are kept confidential.
- All personal information will be password protected and encrypted in a secure database. Staff will have appropriate levels of access.

What are the risks of being included in the database?

- Personal information will be stored in the database however, all information will be secure and will not be accessible to anyone other than the relevant clinic staff.
- Personal identifiers will be retained to ensure accuracy of data as this is clinic database by which your treatment will be managed and delivered.

What are the benefits of being included in the database?

This database forms an integral part of the delivery of your day to day care and will be an important tool for improving the quality of patient care.

What rights do I have?

You may withdraw your consent to be included in the database at any time and request that some or all of your information is removed from the database.

Informed consent form:

I have been asked to participate in the E5 Clinic Haematology Database by the staff of this clinic. I have been given a chance to read the information sheet and to ask questions about the database. These questions have been answered to my satisfaction. I agree to participate in the database. I know that I can withdraw from the database at any time.

Patient sticker:

The Database, including the above information, has been described to me orally. I understand what my involvement in the Database means and I voluntarily agree to participate.

_____ _____

Name AND signature of patient Date

In case of minors or under legal guardianship:

_____ _____

Name AND signature of legal guardian Date

If patient unable to read or write:

Thumb print

_____ _____

Name AND signature of witness Date

If patient needs a translator:

_____ _____

Name AND signature of translator Date
(Where applicable)

_____ _____

Name AND Signature of staff member Date

Appendix B: Human Research Ethics Committee Approval

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

Room 45 E-52-E-Floor- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-submissions@uct.ac.za
Website: https://health.uct.ac.za/home/human-research-ethics

25 October 2022

HREC REF: 659/2022

A/Prof E Verburgh
Division of Clinical Haematology
E-5 NGSH
Email: estelle.verburgh@uct.ac.za
Student: sdawood1212@gmail.com

Dear A/Prof Verburgh

PROJECT TITLE: CORRELATION BETWEEN RISK FACTORS AT DIAGNOSIS AND TREATMENT OUTCOMES IN ADULT PATIENTS WITH EARLY-STAGE HODGKIN LYMPHOMA IN CAPE TOWN, SOUTH AFRICA-SUB-STUDY LINKED TO R024/2018-
(MASTERS CANDIDATE-DR SHAKIRA DAWOOD)

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.

Approval is granted for one year until the 30 October 2023.

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)

The HREC acknowledge that the student: Dr Shakira Dawood will also be involved in this study.

Please quote the HREC REF 659/2022 in all your correspondence.

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.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE

Appendix C: Groote Schuur Hospital Approval

Western Cape Government

GROOTE SCHUUR HOSPITAL

Enquiries: Dr Bernadette Eick
e-mail: GSHResearch.Request@westerncape.gov.za

ASSOCIATE PROFESSOR ESTELLE VERBURGH
Division of Clinical Haematology

E-mail: estelle.verburgh@uct.ac.za

Dear A/Prof E Verburgh

RESEARCH PROJECT: Correlation Between Risk Factors at Diagnosis and Treatment Outcomes in Adult Patients with Early-Stage Hodgkin Lymphoma in Cape Town, South Africa

Your recent letter to the hospital refers.

You are granted permission to proceed with your research, which is valid until **30 October 2023.**

Please note the following:

a) Your research may not interfere with normal patient care.
b) Hospital staff may not be asked to assist with the research.
c) **Confidentiality must always be maintained.**
d) No additior mailto:estelle.verburgh@uct.ac.za e incurred as indicated in your Annexure 2 i.e. Lab, consumables or stationery. **If access to TRACK Care/NHLS is required, kindly attach our letter of approval to the application form and approach Information Management to assist with data.**
e) **No patient folders may be removed from the premises or be inaccessible.**
f) Please provide the research assistant/field worker with a copy of this letter as verification of approval.
g) **Should you at any time require photographs of your subjects, please obtain the necessary indemnity forms from our Public Relations Office (E45 OMB or ext. 2187/2188).**
h) Should you require additional research time beyond the stipulated expiry date, please apply for an extension.
i) Please discuss the study with the HOD before commencing.
j) Please introduce yourself to the person in charge of an area before commencing.
k) On completion of your research, please forward any recommendations/findings that can be beneficial to use to take further action that may inform redevelopment of future policy / review guidelines.
l) If the researcher is not GSH staff member, a supernumerary contract is required before commencement of the research.
m) Please contact Michelle Riley (Patient Fees) at ext. 2276 to ascertain if there will be charges for conducting the Research and to obtain a quote or to discuss charges.
n) **Kindly submit a copy of the publication or report to this office on completion of the research.**
o) **At no time should any posters encouraging patients to partake in research, be displayed within a clinical area.**
p) **Please adhere to ALL COVID-19 regulations and Groote Schuur Hospital policies.**

I would like to wish you every success with the project.

Yours sincerely

pp
DR BERNADETTE EICK
CHIEF OPERATIONAL OFFICER
Date: 15 December 2022
C.C. Mr. L. Naidoo, Prof. N. Ntusi, Dr. N. Khumalo, Mr. A. Mohamed

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Observatory, 7935
www.westerncape.gov.za/health

Appendix D: The Journal of Leukemia and Lymphoma – Author Guidelines

Journal of Leukemia and Lymphoma– Instructions to Authors

Original Research Article full structure

Structure

Your paper should be compiled in the following order: title page; abstract; keywords; main text introduction, materials and methods, results, discussion; acknowledgments; declaration of interest statement; references; appendices (as appropriate); table(s) with caption(s) (on individual pages); figures; figure captions (as a list).

Word Limits

Original Research articles – the word count should be approximately 3,500 words, with no more than 6 tables/figures and approximately 40 references.

Style Guidelines

Font

Use Times New Roman font in size 12 with double-line spacing.

Margins

Margins should be at least 2.5cm (1 inch).

Title

Use bold for your article title, with an initial capital letter for any proper nouns.

Abstract

Indicate the abstract paragraph with a heading or by reducing the font size. The abstract must be no longer than 250 words.

Keywords

Keywords help readers find your article, so are vital for discoverability. If the journal instructions for authors don't give a set number of keywords to provide, aim for five or six.

Formatting and Templates

Papers may be submitted in Word format. Please do not submit your paper as a PDF. Figures should be saved separately from the text. To assist you in preparing your paper, we provide formatting template(s).

Checklist: What to include

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5. Funding details. Please supply all details required by your funding and grant-awarding bodies as follows:

   For single agency grants

   This work was supported by the [Funding Agency] under Grant [number xxxx].

   For multiple agency grants

   This work was supported by the [Funding Agency #1] under Grant [number xxxx]; [Funding Agency #2] under Grant [number xxxx]; and [Funding Agency #3] under Grant [number xxxx].
6. Disclosure statement. This is to acknowledge any financial or non-financial interest that has arisen from the direct applications of your research. If there are no relevant competing interests to declare please state this within the article, for example: *The authors report there are no competing interests to declare*. Further guidance on what is a conflict of interest and how to disclose it.
7. Data availability statement. If there is a data set associated with the paper, please provide information about where the data supporting the results or analyses presented in the paper can be found. Where applicable, this should include the hyperlink, DOI or other persistent identifier associated with the data set(s). Templates are also available to support authors.
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submission. You will be asked to provide the DOI, pre-reserved DOI, or other persistent identifier for the data set.

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