



**THE FEASIBILITY OF INTRODUCING A HARMONISED
TREATMENT REGIMEN, COMPARING AFFORDABLE BLOOD
TESTS AND PET-CT SCANS, TO IMPROVE TWO-YEAR SURVIVAL
RATES IN CHILDREN, ADOLESCENTS AND YOUNG ADULTS
WITH HODGKIN LYMPHOMA IN SOUTH AFRICA**

Original published work and integrated thesis submitted

by

Jennifer Ann Geel

In fulfilment of the requirements for the degree
Doctor of Philosophy in the School of Clinical Medicine, Faculty of Health Sciences,
University of the Witwatersrand

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DECLARATION

I, Jennifer Ann Geel, hereby declare that by submitting this thesis, I confirm that the content contained therein is my original work. I affirm that I am the rightful owner of the authorship unless explicitly stated otherwise. This thesis is being submitted for the Degree of PhD at the University of the Witwatersrand, Johannesburg, and it has not been submitted for any degree or examination at any other university.



(Signature of candidate)

_____ day of _____ 20____ in _____

DEDICATION

I dedicate this work to my family: Thandi, Tamai and Senzo Lewin, for their patience,
humour and encouragement throughout this process

and

to our patients who were thrilled to contribute to science by being part of this study.

Presentations arising from this research project

Oral presentations

1. Geel JA, Hramyka A, Du Plessis J, Goga Y, Van Zyl A, Hendricks MG, Naidoo T, Mathew R, Louw L, Carr A, Neethling B, Schickerling TM, Omar F, Du Plessis L, Madzhia E, Netshituni V, Eyal KC, Ngcana TVZ, Kelsey T, Ballot DE, Metzger ML. Interim analysis changes in erythrocyte sedimentation rate, albumin and lactate dehydrogenase to predict PET response in Hodgkin lymphoma.
55th Annual Conference of the International Society of Paediatric Oncology, Ottawa, Canada October 2023

(One of the top six highest scoring abstracts, winner of Global Health section)

2. Geel JA, Hendricks MG, Goga Y, Neethling B, Netshituni V, Mathew R, Vermeulen J, Van Zyl A, Omar F, Du Plessis J, Madzhia E, Du Plessis L, Ngcana T, Naidoo T, Louw L, Ballot DE, Metzger ML.
A national harmonised protocol for classical Hodgkin lymphoma results in improved survival rates of children and adolescents in South Africa
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3. Hendricks MG, Cois A, Geel JA, Van Heerden J, Donald KA, Kruger M.
Socio-economic status is a determinant of childhood cancer outcome in South African children
54th Annual Conference of the International Society of Paediatric Oncology, Barcelona, Spain, September 2022

4. Geel JA, Hendricks MG, Ngcana T, Omar F, Goga Y, Neethling B, Netshituni V, van Zyl A, Madzhia E, Mathew R, Ballot DE, Naidoo T, Louw L, Metzger ML. Improved survival rates of children and adolescents with classical Hodgkin lymphoma treated on a national harmonised protocol in South Africa.
14th Biennial Continental Meeting of SIOP in Africa, Kampala, March 2022

5. Geel JA. Adapted treatment regimens: Hodgkin lymphoma in South Africa
Annual Congress of Egyptian National Cancer Institute, Cairo University, November 2021
6. Geel JA. Hodgkin Lymphoma. Trials and Tribulations in a Middle-Income Country
(Invited speaker)
International Symposium on Childhood, Adolescent and Young Adult Hodgkin Lymphoma (ISCAYAHL), Berlin, June 2021 (online)
7. Geel JA, Hendricks MG, Eyal KC, Goga Y, Stones DK, Netshituni V, Vermeulen J, Van Zyl A, Madzhia E, Van Emmenes B, Neethling B, Du Plessis L, Naidu G, Omar F, Ballot DE, Metzger M. Strategies to harmonise Hodgkin lymphoma treatment for children, adolescents and young adults in South Africa. Multi-centre collaboration is possible.
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8. Geel JA, Hendricks M, Eyal K, Goga Y, Stones D, Netshituni V, Vermeulen J, Van Zyl A, Madzhia E, Van Emmenes B, Du Plessis L, Naidu G, Omar F, Ballot D, Metzger M. Harmonisation of Hodgkin lymphoma treatment for children, adolescents and young adults in South Africa. Action Research.
50th Annual Conference of the International Society of Paediatric Oncology SIOP, Kyoto, November 2018
9. Geel JA, Hendricks M, Eyal K, Goga Y, Stones DK, Netshituni V, Vermeulen J, Van Zyl A, Madzhia E, Van Emmenes B, Neethling B, Du Plessis L, Naidu G, Omar F, Ballot D, Metzger M. Harmonisation of Hodgkin lymphoma management in children, adolescents and young adults in South Africa
CANSA Research in Action Conference, Pretoria, July 2018
10. Geel JA, Eyal K, Rowe B, Chirwa T, Van Heerden J, Omar F, Stones DK, Goga Y, Stefan C, Van Emmenes B, Wedi O, Vaithilingum M, Van Zyl A, Hendricks M.
Human Immunodeficiency Virus and autoimmune disorders are associated with lower survival rates in children treated for Hodgkin lymphoma in South Africa.

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Posters

1. Geel JA, Kelsey T, Hramyka A, Hendricks MG, Myezo KH, Ngcana TVZ, Van Zyl A, Neethling B, Madzhia E, Mathews R, Goga Y, Netshituni V, Omar F, Ballot DE, Metzger ML. Repurposing “old” blood tests to replace costly interim analysis imaging of Hodgkin lymphoma in low- and middle-income settings.
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2. Geel JA, Myezo KH, Hendrick MG, Ngcana TVZ, Omar F, Goga Y, Neethling B, Rowe B, Netshituni V, Van Zyl A, Ballot D, Metzger M. Multicentre national clinical research in the LMIC setting. Can South Africa produce quality research?
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Peer-reviewed Publications arising from this research project

1. Geel JA, Hramyka A, Du Plessis J, Goga Y, Van Zyl A, Hendricks MG, Mathew R, Louw L, Carr A, Neethling B, Schickerling TM, Omar F, Du Plessis L, Madzhia E, Netshituni V, Eyal KC, Ngcana TVZ, Kelsey T, Ballot DE, Metzger ML for the South African Children's Cancer Study Group. Machine Learning to Predict Interim Response in Pediatric Classical Hodgkin Lymphoma Using Affordable Blood Tests *JCO Glob Oncol*. 2024 Oct;10:e2300435. doi: 10.1200/GO.23.00435. Epub 2024 Oct 24
2. Geel JA, Hendricks MG, Goga Y, Carr A, Neethling B, Netshituni V, Mathew R, Van Zyl A, Omar F, Du Plessis J, Madzhia E, Du Plessis L, Ngcana T, Schickerling T, Naidoo T, Louw L, Kelsey T, Ballot DE, Metzger ML for the South African Children's Cancer Study Group. Improved survival of children and adolescents with classical Hodgkin lymphoma treated on a harmonised protocol in South Africa. *Pediatric Blood and Cancer*. 2023 Oct 9:e30712. doi: 10.1002/pbc.30712
3. Hendricks M, Cois A, Geel J, van Heerden J, Dandara C, Mohamed K, Donald KA, Kruger M.
Socio-economic status significantly impacts childhood cancer survival in South Africa. *Pediatr Blood Cancer*. 2023 Dec;70(12):e30669. doi: 10.1002/pbc.30669. Epub 2023 Sep 13. *Pediatric Blood and Cancer* August 2023
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4. Geel JA, Hendricks MG, Goga Y, Neethling B, Netshituni V, Mathew R, Vermeulen J, van Zyl A, Omar F, du Plessis J, du Plessis L, Madzhia E, Ngcana T, Naidoo T, Louw L, Ballot DE, Metzger M.
SACCSG-HL-2018. Barriers and enablers of a harmonized treatment protocol for childhood and adolescent Hodgkin lymphoma in South Africa. *Pediatric Hematology and Oncology* 20 Jan 2023 DOI: 10.1080/08880018.2022.2162651
5. Geel JA, Eyal K, Hendricks MG, Myezo KH, Stones DK, Omar F, Goga Y, Van Zyl A, Van Emmenes B, Vaithilingum M, Irusen S, Bandini RM, Wedi O, Rowe B, Ballot DE, Metzger M.

Prognostic factors affecting survival in children and adolescents with HIV and Hodgkin lymphoma in South Africa. *Leukemia and Lymphoma*. 2020 Dec 7:1-14. doi: 10.1080/10428194.2020.1852472. PMID: 33284043

6. Geel JA, Chirwa TC, Rowe B, Eyale KC, Omar F, Stones DK, Goga Y, Stefan C, Van Zyl A, Van Emmenes B, Wedi O, Vaithilingum M, Hendricks M. Treatment Outcomes of Children with Hodgkin Lymphoma between 2000 and 2010. First Report by the South African Children's Cancer Study Group (SACCSG). *Pediatric Blood and Cancer* 2017; Apr 6. doi: 10.1002/pbc.26536.

Participation in and contribution to online treatment guidelines based on this project:

ARIA, Hodgkin lymphoma

<https://stg-global.stjude.org/en-us/tools/sj-cares-tools/aria-guide.html>

The Adapted Resource and Implementation Application (ARIA) Guide is a free, online clinical resource that addresses the global need for comprehensive, resource-adapted guidance on the treatment of childhood and adolescent cancers.

I participated as part of an expert team with colleagues from all continents to create a management guideline for paediatric Hodgkin lymphoma.

NCCN Harmonised guidelines for sub-Saharan Africa, Hodgkin lymphoma

<https://www.nccn.org/global/what-we-do/harmonized-guidelines>

National Comprehensive Cancer Network (NCCN) guidelines are positioned as a standard resource for clinical decision-making. Funded by the American Cancer Society and in collaboration with the African Cancer Coalition and the SIOP Africa (International Paediatric Oncology Society, Africa branch) the “NCCN Harmonized Guidelines” are targeted regional resources created by local experts. They represent the ideal healthcare that regions with limited resources aim to deliver, incorporating practical strategies to enhance the accessibility of viable treatment choices.

I chaired the working group for paediatric Hodgkin lymphoma to harmonise the latest North American guidelines with sub-Saharan African capacity.

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Nomenclature

ABVD	Doxorubicin, Bleomycin, Vinblastine, Dacarbazine
ABVD-ChlVPP	Doxorubicin, Bleomycin, Vinblastine, Dacarbazine – Chlorambucil, Vinblastine, Prednisone, Procarbazine
ABVE-PC	Doxorubicin, Bleomycin, Vincristine, Etoposide, Cyclophosphamide, Prednisone
ARIA	Adapted Resource and Implementation Application
ASCT	Autologous Stem Cell Transplant
AMG	Adapted Management Guideline
ATR	Adapted Treatment Regimen
AUC	Area Under the Curve
BEACOPP	Bleomycin, Etoposide, Doxorubicin (Adriamycin), Cyclophosphamide, Vincristine (Oncovin), Procarbazine, Prednisolone
BV	Brentuximab-Vedotin
CAYA	Children, Adolescents and Young Adults
CAYAHL	Childhood, Adolescent and Young Adult Hodgkin Lymphoma
CD4	Cluster Determinant 4
CHBAH	Chris Hani Baragwanath Academic Hospital
cHL	Classical Hodgkin Lymphoma
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
COG	Children’s Oncology Group
COPDac	Cyclophosphamide, Vincristine, Prednisone, Dacarbazine
CR	Clinician-Researcher
DECA	Dexamethasone, Etoposide, Cisplatin, Cytarabine
EFS	Event-Free Survival
FDG	Fluoro-Deoxy Glucose
GFAOP	Groupe Franco-Africain d’Oncologie Pédiatrique
GICC	Global Initiative for Childhood Cancer
HIC	High-Income Country/Countries
HIV	Human Immunodeficiency Virus
HL	Hodgkin lymphoma (includes nodular lymphocyte predominant type)
HREC	Health Research Ethics Committee
IFRT	Involved field Radiotherapy
LMIC	Low- and Middle-Income Countries
MOPP	Nitrogen mustard, Vincristine, Procarbazine, Prednisone
MOMP	Methotrexate, Vincristine, Cyclophosphamide, Prednisone
NCCN	National Comprehensive Cancer Network
NHRD	National Health Research Database
OEPA/OPPA-COPP	Vincristine, Etoposide, Prednisone, Doxorubicin/ Vincristine, Procarbazine, Prednisone, Doxorubicin- Cyclophosphamide, Vincristine, Procarbazine, Prednisone
OS	Overall Survival
PD1	Programmed Cell Death Protein 1
PDL1	Programmed Cell Death Ligand 1
PET-CT	Positron Emission Tomography-Computer Tomography
PFS	Progression-Free Survival
PI	Principal Investigator
POU	Paediatric Oncology Unit
REDCap	Research Electronic Data Capture

ROC	Receiver Operating Characteristic
SACCSG	South African Children's Cancer Study Group (recently changed to SAAPHO, South African Association of Paediatric Haematology Oncology)
SAHPRA	South African Health Products Regulatory Agency
SDG	Sustainable Development Goals
VAMP	Vincristine, Doxorubicin, Methotrexate, Prednisone
WDGMC	Wits Donald Gordon Medical Centre

Abstract

Paediatric classical Hodgkin lymphoma (cHL) is highly curable using chemotherapy and radiotherapy. Prior to this study, no collaborative, prospective cHL studies had been performed in South Africa. The retrospective assessment informed the creation of the prospective harmonised guideline. We aimed to determine a baseline survival rate and prognostic factors; explore reasons for mortality in HIV-positive patients, assess the feasibility of introducing a harmonised treatment guideline, prospectively assess survival and analyse the prediction of chemosensitivity at interim assessment.

In the retrospective analysis, multiple potential prognostic factors were analysed and survival rates calculated with Kaplan-Meier curves and Cox regression analysis. An initial survey was conducted of the clinical researchers before the launch of the prospective study, followed by a mid-study assessment. Two-year overall survival was calculated by Kaplan-Meier curves and computer-learning models were utilised to compare chemosensitivity based on interim PET-CT assessment with changes in haematological and non-specific markers of disease activity.

The retrospective analysis accrued 294 patients, of whom 29 were HIV-positive. The 5-year overall survival was 84% in HIV-negative and 49% in HIV-positive patients. Advanced stage, HIV infection and treatment with regimens other than doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) were associated with lower survival rates. In HIV-positive patients, an AIDS-defining CD4 count and hypoalbuminaemia were associated with poorer prognosis. The pre-study assessment indicated that the majority of centres fulfilled all criteria to participate in the study. The mid-study assessment identified barriers to participation and methods to mitigate these challenges.

Analysis of 132 prospectively accrued patients (19 HIV-positive, 113 HIV-negative) treated on a risk-stratified, response-adjusted treatment regimen resulted in higher survival rates of 93% in HIV-negative and 89% in HIV-positive patients. Changes in low-cost, widely available blood tests correctly predicted chemosensitivity, identifying patients who may not require radiotherapy.

In conclusion, higher survival rates for paediatric cHL were documented following the introduction of a harmonised management guideline in South Africa. In settings that do not have access to PET-CT, changes in affordable blood tests may be used to substitute for

radiological interim assessment, although a format suitable for individual patients is yet to be developed for the clinical setting.

This research marks the inaugural collaborative effort where patients from every South African paediatric oncology unit and the majority of private paediatric oncology practices, were afforded the opportunity to participate in a prospective study aimed at enhancing survival rates.

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Nature and scope of contributions

Jennifer Geel: I conceptualised this thesis with my supervisors. I developed the study protocol, including the development of the management algorithm, choice of chemotherapy, doses of radiotherapy, formulation of the questionnaires, writing of standard operating procedures and data collection. I trained the research assistants and collaborating clinician-researchers in data collection and capture, and was available to discuss challenging cases, assisting them to make appropriate treatment decisions. I performed data capture of the patients in the Wits circuit, as well as those in certain centres who experienced challenges. I recruited the patients at two hospitals and undertook all quality control of data management and worked with the collaborating statisticians. I wrote the five articles for publication.

Monika Metzger supervised conceptualisation of the prospective study protocol including the management algorithm, assisted in the concept development of all studies, critically reviewed and approved publication manuscripts.

Daynia Ballot supervised conceptualisation of the prospective study protocol, assisted in concept development of all studies, critically reviewed and approved publication manuscripts.

Tom Kelsey assisted in protocol development to ensure that the appropriate statistical concepts were incorporated, critically reviewed and edited all data-related reporting contained in the manuscripts for Chapters 5 and 6.

Artsiom Hyramyka applied the statistical principles and analysed data, contributing to the manuscripts for Chapters 5 and 6.

All co-authors critically reviewed manuscripts and agreed that the material could be used for this PhD thesis. Collaborating authors in each paediatric oncology unit played different roles which included agreeing on the management algorithm, design of the prospective study, data collection and co-authorship of the resulting publications.

Plagiarism declaration

This thesis has been submitted to the Turnitin module and I confirm that my supervisors have seen my report and any concerns revealed by such have been resolved with my supervisors.

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Definition of terms

Adapted treatment regimen ¹	Represents efforts to improve care for each disease adapted to local resources. Adapted regimens are best applied in conjunction with a data management programme and frequent and rigorous outcome evaluation to determine whether the regimen is achieving the expected results.
Children, Adolescents and Young Adults (CAYA) ^{2,3}	Term used in the Childhood, Adolescent and Young Adult Hodgkin Lymphoma (CAYAHL) group. Refers to both patients and survivors to ensure that the unique needs of these age groups are met.
Clinician-researchers ⁴	Clinicians who take part in clinical research. In this context paediatric haematologists and oncologists.
Harmonisation ⁵	Refers to a growing effort by global oncologists to employ the same standards and norms in diagnosing and treating various cancers. The term may also include the minimising of redundant or conflicting standards which might have evolved independently.
Hodgkin lymphoma ⁶	Encompasses both classical HL (cHL) and nodular lymphocyte predominant HL (NLPHL), now considered a separate subtype
Paediatric oncology unit	A dedicated unit in the public sector that treats children with cancer. The multidisciplinary team is generally led by the paediatric oncologist/haematologist. Certain POU's are able to treat adolescents and young adults, according to institutional regulations.
Research protocol ⁷	Detailed plan of a research study designed to answer a specific scientific question. May incorporate clinical guidelines.
Treatment guidelines (clinical practice guidelines) ⁸	Recommendations on diagnosis and treatment, intended to ensure that all patients receive standardised, appropriate treatment and care. Guidelines summarise current medical knowledge, weigh the benefits and harms of diagnostic procedures and treatments, and give specific recommendations using the existing evidence base. Clinical practice guidelines are considered standard of care and should be updated regularly.

Chapter 1. Introduction

1.1 Background

1.1.1 Overview

Over the past fifty years, significant strides in the management of childhood and adolescent cancer have yielded remarkable outcomes, particularly in high-income settings, where the overall 5-year survival rate now surpasses 80%.⁹ Notably, Hodgkin lymphoma, which remained largely untreatable from its description in the 17th century until the mid-20th century, has undergone a similar transformation, mostly in well-resourced settings.^{10,11} and long-term survival rates over 95% have been reported by certain cooperative groups.^{12–14}

In 2018, the WHO Global Initiative for Childhood Cancer (GICC) was launched, with the overarching aim of improving global childhood and adolescent cancer survival rates to 60% by 2030.¹⁵ As part of this initiative, six tracer cancers were identified as being highly curable and relatively common. These cancers comprise 50-60% of all childhood and adolescent cancers, and include acute lymphoblastic leukaemia, low-grade glioma, nephroblastoma, retinoblastoma, Burkitt lymphoma and Hodgkin lymphoma.¹⁵ This initiative aims to bridge the gap in survival rates among different parts of the world. These tracer cancers represent both the potential for successful treatment outcomes and the concerted efforts towards improving the landscape of childhood and adolescent cancer care on a global scale.

In the South African state hospital context, adolescents may be treated in either paediatric or adult units, depending on the regulations of the particular hospital. In this study we have included children, adolescent and young adult patients as adolescents and young adults have been shown to have higher survival rates on “paediatric” treatment protocols¹⁶ and it has become increasingly common to treat this wider age-group with similar treatments.^{2,17} The term CAYA encompasses children, adolescents and young adults and is used in this thesis to include all these patients, except when only children and/or adolescents are indicated. There is considerable overlap between findings of adult and paediatric studies, and it is thus necessary to examine literature on adult patients as well as children and adolescents.

1.1.2 Definition

Classical HL (cHL) is a malignancy originating in the lymphatic system, currently thought to be a disorder of immune dysregulation, affecting children, adolescents and adults.⁶ It is a relatively slow-growing cancer with a predictable clinical presentation. cHL comprises the subtypes nodular sclerosing, mixed cellularity, lymphocyte depleted and lymphocyte rich, while nodular lymphocyte predominant HL is in a separate category.

1.1.3 Epidemiology

The epidemiology of CAYA cHL is poorly described in low- and middle-income countries (LMIC) due, in part, to lack of high-quality cancer registries. However, it has been documented that the age at presentation is younger in patients in LMIC than in high-income countries (HIC), and it is more likely to be associated with Epstein-Barr virus infection in these settings.¹⁸ cHL is more common in males than females, and the incidence rises with age. In the United States, cHL is the most commonly diagnosed cancer in adolescents aged 15-19 years. The most recent age-standardised rate (ASR) in the USA is 5.8 per million.¹⁹ In South Africa, the reported ASR was 2.2 per million, in a study based on data up to 2007 while more representative data from the national cancer registry reports an ASR of 2.87 in 2019.^{20,21} The lower incidence rates may in part be explained by underdiagnosis, misdiagnosis or under-reporting.

1.1.4 Diagnosis

cHL is characterised by a monoclonal proliferation of lymphoid cells, encompassing both mononuclear Hodgkin cells and multinucleated Reed-Sternberg cells. These distinct entities, known as Hodgkin Reed-Sternberg cells, can be observed in varying quantities amidst an immunoreactive milieu comprising neutrophils, lymphocytes, eosinophils, histiocytes, plasma cells, fibroblasts and collagen.²² cHL is unique in that the malignant cell, the Reed-Sternberg cell, represents only a small proportion of cells constituting the bulk of the tumour.⁶

Diagnosis relies on morphological examination of an excised lymph node with interpretation of immunohistochemical stains. While cHL can be diagnosed on fine needle aspiration cytology (FNAC),^{23,24} this requires a comprehensive history to be provided to a pathologist experienced in the diagnoses of paediatric malignancies, and cHL in particular. False negatives and false

positives are common, and the preferred modality is lymph node excision biopsy to make the definitive diagnosis.²⁵ This requires functional paediatric surgery facilities, not widely available in the LMIC setting.²⁶ Although HL may be diagnosed in bone marrow trephine biopsy, this is considered suboptimal as it is not possible to differentiate between nodular lymphocyte predominant HL and the four subtypes of cHL, an essential distinction.²⁷

1.1.4 Staging and risk stratification

An effective staging and risk stratification system should correlate with survival outcomes, and facilitate treatment modifications to maximise the patient's chance of survival.²⁵ The Ann Arbor staging system was finalised in 1971 for both Hodgkin and non-Hodgkin lymphoma, replacing the Rye staging system and later amended with the Cotswolds additions.^{28,29} As treatment combinations have grown more effective, the staging systems that meticulously evaluate the locations and dimensions of disease have been incorporated into risk classification systems which are intended to tailor treatment intensity according to prognosis.²⁵

Over time, staging assessments have progressed from clinical evaluations based on lymph node size and chest X-ray assessments of mediastinal masses to more advanced techniques such as computed tomography (CT) or magnetic resonance imaging (MRI) scans to evaluate sizes and locations of supra- and infra-diaphragmatic nodal masses. Metabolic activity was historically assessed by gallium scans,³⁰ and then replaced by positron emission tomography-computerised tomography (PET-CT) scans, which can define the anatomical size and location of lesions as well as metabolic activity in one procedure.⁶

The classification into standard/low, medium/intermediate, and high-risk groups varies slightly among different cooperative groups; however, the overarching objective remains consistent – accurately identifying patients who would benefit from intensified treatment to maximise their chances of survival, while avoiding overtreatment of lower risk patients.³¹

The capacity to stage- and risk-stratify patients precisely depends on the availability of radiology (X-ray, ultrasound, CT and MRI), nuclear medicine (PET-CT or gallium scanning), haematology (full blood count and bone marrow trephine morphology) and pathology (bone marrow biopsy). The current gold-standard approach includes clinical assessment of B symptoms, combined with an erect chest X-ray to assess the size of mediastinal masses and a PET-CT to detect anatomical and functional assessments of malignant masses. In the era of

PET-CT, bone marrow trephine biopsies are no longer considered essential for staging,³² but as the majority of African countries do not have the capacity to perform PET-CT scans,³³ trephine biopsies continue to be used to stage patients accurately.

Most reports in sub-Saharan Africa do not incorporate risk stratification but rather report on Ann Arbor staging,^{34–37} while cooperative groups in North Africa^{37,38}, Europe and North America routinely use risk stratification.² These risk stratification systems have not been harmonised worldwide and there is some overlap, especially in the assignment of Ann Arbor Stage II and III patients, some of whom are placed in the medium-risk category and some in the high-risk category (see Table 1).

Standardisation of initial staging criteria is required to facilitate comparison of results across different studies. Differences between prominent European and North American collaborative groups include definitions of splenic involvement, sizes of pulmonary and hepatic lesions and definitions of extranodal involvement. It is recommended by the Childhood, Adolescent and Young Adult Hodgkin Lymphoma (CAYAHL) group that details of each criterion should be clearly defined to increase standardisation.² However, in settings that lack access to the required modalities, alternative harmonisation of initial staging and response-assessment is yet to take place.

Table 1. Variation in risk stratification across paediatric Hodgkin lymphoma cooperative groups and study protocols.

Study group/institution	Region	Risk group	IA	IB	IIA	IIB	IIIA	IIIB	IVA	IVB
(COG) ^{39,16,40}	North America	Low								
		Intermediate	E		E					
		High								
Pediatric HL Consortium ⁴¹	North America	Low								
		Intermediate	E, X		E, X					
		High								
EuroNet-PHL-C1 ⁴²	Europe	Low								
		Intermediate	E/RF	E/RF	E/RF					
		High				E	E			
EuroNet-PHL-C2 ⁴³	Europe	Low								
		Intermediate	E/RF	E/RF	E/RF					
		High				E	E			
InPOG ⁴⁴	India	Early								
		Advanced								
GFAOP ⁴⁵	Francophone Africa	Favourable								
		Unfavourable								
MSPHO ³⁷	Morocco	Favourable								
		Unfavourable	E/RF	E/RF	E/RF	E/RF				
Cairo University ⁴⁶	Egypt	Low								
		Intermediate	RF	RF	RF	RF				
		High					RF			
SACCSG ⁴⁷	South Africa	Low/standard								
		Medium/intermediate	X/E	X/E	X/E	X/E				
		High					X+E	X+E		

COG: Children's Oncology Group; E: extranodal extension; X: bulky disease (peripheral lymph nodal mass >6cm or mediastinal mass > 33% of mediastinal diameter); RF: risk factors comprising erythrocyte sedimentation rate > 30 mm/hr and/or bulk ≥ 200 mL; InPOG: Indian Paediatric Oncology Group; GFAOP: Groupe Franco-Africain d'Oncologie Pédiatrique; SACCSG: South African Children's Cancer Study Group. Moroccan Society of Pediatric Oncology and Hematology

1.1.5 Early treatments for Hodgkin lymphoma

RADIOTHERAPY

Early therapeutic approaches were formulated in North America. The application of X-ray therapy for HL was initially documented in 1902, used on a young adult male and a 4-year-old boy, both of whom exhibited remarkable clinical responses.⁴⁸ Radiation was applied from a distance of 5 cm to the clinically evident nodal masses, which could be considered an early form of nodal radiotherapy. Despite this promising initial start, the responses were either incomplete or of insufficient duration, and radiation fields were therefore expanded to encompass the neighbouring clinically unaffected lymph node regions.⁴⁹ Between 1920 and 1940, radical surgery with or without radiotherapy was used to treat localised disease,⁵⁰ but it became clear that surgery failed to prolong survival and led to its gradual discontinuation in favour of radiotherapy alone.⁵¹

In the 1950s and '60s, megavoltage radiotherapy emerged as a method to treat large volumes of the body with higher doses.⁵² Radiotherapy techniques underwent further development, resulting in the emergence of involved field techniques, such as the mantle field which aimed to treat contiguous lymph node areas¹¹ (see Figure 1). These fields have been refined to include smaller and smaller areas to prevent long term effects such as cardiac dysfunction, breast and thyroid cancers in survivors.^{53–55}

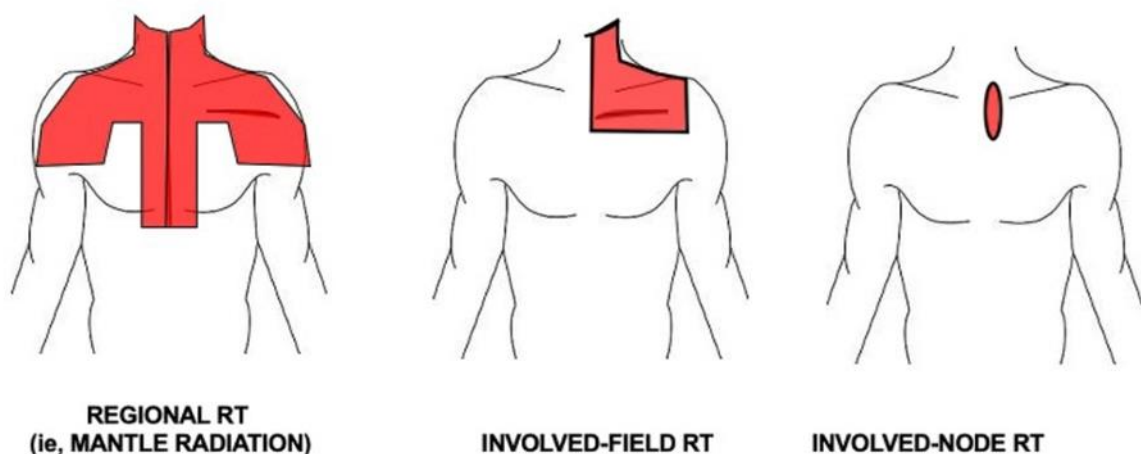


Figure 1. The evolution of radiotherapy fields for early-stage Hodgkin lymphoma.

(Included with kind permission of Aznar et al)⁵³

The introduction of combined modality therapy as the primary treatment for limited stage Hodgkin lymphoma brought significant changes in recommended radiotherapy dosage and fields.¹¹ Prospective trials demonstrated the efficacy of limited field treatment combined with chemotherapy.^{56–58} Involved site and involved node radiotherapy approaches were introduced, using smaller radiation fields based on improved disease localisation and better systemic disease control with chemotherapy. Pre-treatment PET-CT and interim assessment PET-CT (iPET-CT) imaging are now considered essential for accurate assessment and radiotherapy voltage and field design.⁵²

HISTORICAL OVERVIEW OF DESIGN OF CHEMOTHERAPY REGIMENS

Single-agent nitrogen mustard demonstrated short-term effects^{59,60} in 1963 and the first combination chemotherapy regimen was reported in 1967, using the principles of multi-agent chemotherapy pioneered in the treatment of acute lymphoblastic leukaemia.⁶¹ Components of multi-agent regimens included alkylators (procarbazine, dacarbazine and cyclophosphamide), intercalating agents and topoisomerase II inhibitors (doxorubicin), antimetabolites which inhibit DNA synthesis (methotrexate, bleomycin) and disruption of the mitotic spindle (vincristine, vinblastine) with prednisone, the precise mechanism of which remains unclear.

Ensuing combinations trialled in adults included MOMP (methotrexate, vincristine, cyclophosphamide and prednisone)⁶¹ and MOPP (nitrogen mustard, vincristine, procarbazine, prednisone)⁶². In the 1960s, the first prospectively randomised trials were run, initially comparing radiotherapy alone to combination chemotherapy, and later exploring combinations of multimodality therapy to determine the most effective radiotherapy dosing in combination with chemotherapy. The growth-inhibitory effects of high-dose radiotherapy in children later became apparent, leading to the use of lower dose radiotherapy combined with multi-agent chemotherapy in the Stanford V regimen, resulting in a ten-year OS (overall survival) of 89%.⁶³

A trial comparing MOPP to subtotal nodal radiotherapy demonstrated superior results with MOPP.⁶⁴ However, MOPP was later associated with the development of second malignant neoplasms, male sterility and accelerated ovarian aging.⁶⁵ Additionally, a large number of patients did not experience complete remission with MOPP, and relapses occurred in up to 30% of complete responders^{66,67} prompting the search for more effective, less toxic regimens.

The combination of doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) was developed in Italy based on evidence of the anti-lymphoma properties of all four drugs and their non-overlapping sensitivity profiles with MOPP. ABVD was found to be equivalent to or better than MOPP in efficacy⁶⁸ but late effects differed: there was an increased incidence of cardiotoxicity due to the anthracycline doxorubicin in ABVD, particularly when combined with mediastinal irradiation.⁶⁹

Researchers then attempted to address the issues of non-responders and treatment toxicity through modified treatment regimens such as MOPP/ABVD⁷⁰ and ABVD-ChlVPP⁷¹. These treatments were further modified for children by reducing radiation dose and field size and relying on chemotherapy across all disease stages.⁷² Cooperative trial groups initiated studies in the late 1970s, demonstrating successful treatment of children with cHL, with long-term survival rates above 90%.⁷³ In the 1980s, German researchers demonstrated 5-year OS rates of 98% using OPPA/COPP.^{56,74} Specific trials then focused on eliminating procarbazine due to its gonadotoxicity, incorporating dose-dense chemotherapy cycles, and evaluating treatment adaptations based on response. Trials using OEPA-COPP and OEPA-COPDac successfully replaced procarbazine with etoposide and maintained high OS.^{57,73}

During the past three decades, collaborative groups have devised different treatment approaches for paediatric cHL. Most European and North American study groups have favoured combinations of chemotherapy and radiotherapy, while South American groups have initially pursued chemotherapy-only regimens due to the lack of radiotherapy facilities in these resource-constrained settings.⁷⁵

In 2014 the North American Children's Oncology Group (COG) reported a strategy of tailoring therapy based on interim response assessment. They omitted radiotherapy in patients with rapid early response and complete response at the end of treatment while augmenting chemotherapy in patients with slow early response.³⁹ This study used doxorubicin, bleomycin, vincristine, etoposide, cyclophosphamide, and prednisone (ABVE-PC) and dexamethasone, etoposide, cisplatin, and cytarabine (DECA).

Later COG trials focused on early-stage disease and reduced systemic chemotherapy while incorporating response-adapted involved field radiotherapy (IFRT), demonstrating both safety and efficacy, with improved survival rates reported in 2018.³⁹ Brentuximab vedotin (BV), first tested in adults, gained increasing acceptance in high-risk paediatric cHL, showing efficacy in

improving survival rates and establishing BV as a standard treatment option in high-income countries.⁷⁶ Other agents now in use in paediatric cHL include pembrolizumab⁷⁷ and nivolumab⁷⁸. These agents are currently unavailable in the state sector in South Africa,⁷⁹ and there is limited availability in the private sector.

It is clear that traditional chemotherapy agents can yield high cure rates, particularly in resource-constrained settings with limited access to newer, costly agents. This is accomplished through the implementation of long-established treatment regimens that have been in practice for nearly six decades. Such high cure rates had not been demonstrated in South Africa before this study.

RESPONSE ASSESSMENT

In 1999, an International Working Group introduced standardised response criteria for non-Hodgkin lymphoma and HL.⁸⁰ These guidelines outlined various response categories from complete remission to progressive disease determined through assessments which included physical examination, chest x-rays, computed tomography (CT) scans, gallium scans and visual evaluations of bone marrow. Subsequent advancements, such as the introduction of PET scans, led to the 2007 revised guidelines.⁸¹ This updated version included PET scans as an integral element of response evaluation, primarily for HL and diffuse large B-cell lymphoma.

Response assessment criteria⁸² were initially adopted by the adult oncology community and later by paediatric oncologists. Interim assessment has become standard-of-care in the management of paediatric cHL and is used to determine chemosensitivity to decide whether to intensify treatment in the case of refractory disease, consolidate with radiotherapy in the case of residual metabolic activity or forgo radiotherapy in the case of complete metabolic response.⁷² Despite the many trials and studies, response assessment criteria have not been harmonised worldwide.⁷² Due to the limited availability of CT and PET-CT facilities, the ability to assess response is limited in many African countries.³³

1.1.6 Treatment

Successful treatment of cHL in children, adolescents and young adults (CAYA) requires a functional multidisciplinary team approach. Current treatment for cHL in relatively well-resourced settings includes traditional chemotherapeutic agents in various combinations, as

well as immune checkpoint inhibitors such as PD1 and PDL1 inhibitors,⁸³ which are not widely available in South Africa or indeed the rest of Africa. There is no single treatment combination considered suitable for all patients, and established treatment regimens are either adopted by or adapted to the local setting.

1.2 Paediatric Classical Hodgkin lymphoma in Africa

Retrospective reports from North Africa have documented relatively high survival rates for paediatric cHL with 85% 3-year OS in Morocco and 96% 5-year OS in Egypt, both lower-middle-income countries.^{84,85} Prospective data on survival rates for paediatric cHL in Africa is severely limited,⁴⁵ with a dearth of information specifically from sub-Saharan Africa.

Despite the many advances demonstrated in the treatment of paediatric cHL, such success has not previously been reported in South Africa. Single-centre retrospective reviews reporting small numbers documented survival rates of 58-83%⁸⁶⁻⁸⁹ but these studies come from older, more established POUs and can thus not be considered representative of all South African patients. The majority of studies are retrospective, offering valuable insights, but are inherently limited, with the possibility of selection bias, recall bias or misclassification bias. Moreover, the available data regarding CAYA with both cHL and HIV is scarce and largely anecdotal, failing to provide robust prospective insights into this patient population. As South Africa is home to the world's largest group of people living with HIV,⁹⁰ further investigation is warranted to expand our understanding of optimal therapeutic approaches for these patients.

1.3 Rationale for the study

The four pillars of the GICC are National Commitment and Planning, Advocacy and Partnerships, Service Delivery and Monitoring and Evaluation. The WHO GICC operates in alignment with the broader global cancer control agenda, including the WHO Global Cancer Initiative and the Sustainable Development Goals (SDGs). The GICC aims to reduce disparities in childhood cancer outcomes and improve the quality of life for children and adolescents with cancer and their families worldwide.¹⁵ This PhD project aligns with the GICC approach, and thus constitutes application of these principles for the first tracer cancer to be comprehensively addressed in South Africa.

Few prospective, collaborative studies on paediatric cHL are documented in resource-constrained countries.⁶¹ Such studies offer numerous advantages and compelling arguments for their implementation, namely increased sample size, enhanced generalisability, comprehensive data collection, focus on rare diseases, faster accrual, resource sharing, cost efficiency and multidisciplinary collaboration. Through pooling data, we can minimise potential biases and accumulate sufficient cases to investigate rare diseases comprehensively and develop evidence-based guidelines for clinical decision-making. The act of examining the available literature, crafting a locally relevant protocol and sharing best practices raises the national standard of care, ultimately fostering global improvements in treatment outcomes.^{91–93}

Standardised cHL guidelines are frequently used without adaptation in LMIC despite being created for use in HIC with adequate access to excellent supportive care. An example of a HIC practice used in an LMIC setting with potentially poor outcomes, is the use of high-dose methotrexate in the treatment of paediatric haematological malignancies, without access to therapeutic drug monitoring or supportive measures such as leucovorin.⁹⁴ Within certain contexts, the implementation of intensive chemotherapy regimens has yielded unexpected outcomes, with lower rather than higher survival rates being observed. This phenomenon can be attributed to an elevated incidence of treatment-related toxicity.⁹⁵ Nevertheless, evidence suggests that the deliberate introduction of more intensive regimens in a controlled environment can lead to improved survival rates once the issue of treatment toxicity is effectively addressed.⁹⁶

As CAYA cancers in general, and CAYA cHL specifically, are rare, it is common for research in Africa to be based on retrospective studies, and for management decisions to be based on these or on regimens suitable for high-income settings. The utilisation of intensive chemotherapy regimens created for use in HIC in an LMIC context, as well as evaluation primarily through retrospective studies, raises concerns regarding the accurate determination of outcomes and prognostic factors of patients within our specific setting.

Documented OS of childhood and adolescent cancer in South Africa is lower than in many other countries with similar challenges^{84,97,98} and reliance on small institutional reviews or retrospective audits is inadequate to address this issue. Harmonisation of treatment guidelines was a movement that was gaining strength, and collaborative research studies were identified as a vital approach to generate locally derived data.^{2,99} Successive cHL trials have raised survival rates in Europe and USA but this had not been attempted in the South African setting.

Prior to this initiative, risk grouping was not reported or widely applied and response-adapted therapy was not widely practised.^{86,88,89} The persistence of outdated treatment approaches, coupled with the absence of compelling evidence to support alternative approaches, posed challenges in advocating for protocol modifications or changes within the local context. Despite convincing evidence demonstrating the increased harm of extended field radiotherapy, such as the mantle field technique in paediatric patients,⁵² its continued utilisation in numerous South African healthcare centres persisted. In some instances, certain centres persisted in the practice of administering radiotherapy to all patients upon completion of therapy, regardless of treatment response despite compelling evidence indicating the unnecessary nature of this practice.^{13,70,100}

Radiology resources are scarce in many African countries, particularly nuclear medicine facilities that include PET-CT.^{33,101} This prompted the need to consider alternative risk assessment approaches for Hodgkin lymphoma that would be applicable in these regions. The capacity to provide radiotherapy is also severely limited in Africa¹⁰² emphasising the importance of identifying those patients who may not require radiotherapy.

1.4 Research outline

The project encompassed linked retrospective and prospective components. The retrospective component established baseline data on both HIV-positive and --negative patients, identifying treatment regimens in use, survival rates and prognostic factors. This information was used to create a prospectively studied adapted management guideline (AMG) tailored to the local setting. Important considerations included toxicity of the first-line regimen given the restricted access to antibiotics, blood products and intensive care; cost to the treating centre; availability of chemotherapy agents and access to radiotherapy and surgical skills.

1.4.1 Aims

The study aimed to determine baseline survival rates and prognostic factors and to assess if a harmonised treatment protocol incorporating risk stratification and response adaptation, representing an AMG¹⁰³ for an upper-middle income country, was associated with improved survival.

1.4.2 Objectives

The objectives were the following:

1. To identify prognostic factors at presentation that influence 5-year OS in a historical cohort. Potential prognostic factors included B symptoms, Ann Arbor stage, risk group at diagnosis, nutritional status, socio-economic factors, HIV status and levels of non-specific markers.
2. To explore survival rates of CAYA with HIV and cHL in a historical cohort, and to determine prognostic factors.
3. To determine the feasibility of the introduction of a single harmonised management protocol for CAYA with cHL among participating POUs in South Africa.
4. To describe outcomes of patients treated on a single harmonised protocol and to compare outcomes of these patients with those of a historical cohort in the same setting. These outcomes include two-year survival rates (progression-free survival and overall survival) and causes of death.
5. To determine if changes in the levels (absolute levels and/or trends, alone and in combination) of haematological values and non-specific markers were associated with a PET-negative study after two cycles of first-line therapy.

1.4.3 Outline of thesis

This dissertation comprises five hypotheses with the related chapters and publications and describes the chronological development of baseline data, implementation of a nationwide prospective study using a management algorithm for cHL, followed by results.

CHAPTER 2. RETROSPECTIVE REVIEW OF CHL IN SOUTH AFRICA

Prior to the initiation of this study, the absence of standardised treatment protocols in South Africa resulted in the utilisation of diverse regimens by POUs, predominantly based on the familiarity of the treating physicians. These regimens were primarily derived from high-income countries and occasionally adapted by individual POUs. Consequently, there was limited knowledge regarding the specific regimens employed in different settings, associated survival rates and prognostic factors that influenced outcomes.

Objective:

To identify prognostic factors at presentation that influence 5-year OS in a historical cohort. Potential prognostic factors include B symptoms, Ann Arbor stage, risk group at diagnosis, nutritional status, socio-economic factors, HIV status and levels of non-specific markers.

Hypothesis:

In a retrospective cohort, certain factors will have prognostic significance in predicting 5-year OS. These include B symptoms, Ann Arbor stage, nutritional status, socio-economic factors, HIV status and levels of non-specific markers.

This chapter provides a recent historical perspective (2000-2010) on CAYA with cHL in South Africa, describing overall survival, progression-free survival, causes of death and prognostic factors. The findings of this study were used to inform the creation of the prospective treatment protocol.

South Africa has the largest global burden of HIV,⁹⁰ and there are currently no guidelines on the management of paediatric patients with HIV and cHL. Apart from one study that included 12 patients with cHL and HIV, there was no data on this group of patients.¹⁰⁴

Objective:

To explore survival rates of CAYA with HIV and cHL in a historical cohort, and to determine prognostic factors.

Hypothesis:

In a retrospective cohort of patients with HIV and cHL, the 5-year OS will differ from that of the HIV-negative patients. Prognostic factors will include nutritional status, CD4 count/percentage and Ann Arbor stage.

The database created from the national retrospective study was used to conduct a more comprehensive investigation into the reasons for the lower survival rates of CAYA with HIV. The findings of this study were used to inform the treatment of HIV-positive CAYA in the prospective treatment protocol.

Collaborative study groups such as the North American Children's Oncology Group (COG), the European Network for Pediatric Hodgkin Lymphoma (EuroNet-PHL) and the South American Asociación de Hemato-Oncología Pediátrica de Centro América (AHOPCA) have documented increased survival in paediatric cHL using successive studies run by collaborative groups.⁷² The Groupe Franco-Africain d'Oncologie Pédiatrique (GFAOP) has been running prospective studies in Francophone African countries, one of which was a protocol for cHL using a simplified risk-stratification into favourable or unfavourable risk groups.⁴⁵ The Indian paediatric oncology group (InPOG) recently demonstrated success using a harmonised protocol and response-adaptation based on PET-CT.⁴⁴

Prior to this study, it was not known whether a multicentre, national study was feasible in South Africa.

Objective:

To determine the feasibility of the introduction of a single harmonised management protocol for CAYA with Hodgkin lymphoma among participating POUs in South Africa.

Hypothesis:

Implementation and introduction of a single harmonised protocol suitable for all paediatric patients with cHL is feasible in South Africa.

This chapter documents the prospective evaluation of the availability of modalities required to treat paediatric cHL and the capacity of each POU to participate in a multicentre research study. Barriers and enablers were explored by surveying CRs prior to the initiation of the study and again once all sites had started patient recruitment.

The survival rates of both HIV-positive and HIV-negative CAYA with cHL were considered suboptimal (Chapters 2 and 3) and the collaborative group aimed to raise these survival rates by implementing the harmonised treatment guideline across all state facilities with the option of introducing this in the private sector as well.

Objective:

To describe outcomes of patients treated on a single harmonised protocol and to compare outcomes of these patients with those of a historical cohort in the same setting. These outcomes include two-year survival rates and causes of death.

Hypothesis:

The introduction of a harmonised treatment protocol will lead to higher one and two-year survival rates in CAYA treated for Hodgkin lymphoma in South Africa, with the greatest improvement seen in patients treated in previously under-resourced centres.

This chapter documents the results of the prospective introduction of a single harmonised protocol to South Africa. It includes 2-year OS and PFS for HIV-negative and HIV-positive patients, correlation of risk stratification with survival and prognostic factors.

Response-adapted management of cHL with iPET-CT is considered standard-of-care in well-resourced settings but remains unavailable in most African countries. South African laboratories are able to test for multiple non-specific blood markers known to have some prognostic utility in cHL.

Objective:

To determine if changes in the levels (absolute levels and/or trends, alone and in combination) of haematological values and non-specific markers are associated with a PET-negative study after two cycles of first-line therapy.

Hypothesis:

The changes in a combination of available blood tests at interim assessment (2 cycles) are as useful as the changes seen on PET-CT at interim assessment in assessing early response to chemotherapy in CAYA in South Africa.

This chapter documents the correlation between changes in non-specific markers and haematological values with interim PET-CT response in 17 South African POU's.

CHAPTER 7: INTEGRATED DISCUSSION AND CONCLUSION

This chapter discusses the results of the individual papers in context and outlines recommendations for future practice and research in the field.

1.5 Methodology

1.5.1 Setting

The multicentre study was coordinated from Johannesburg, in the University of the Witwatersrand circuit. The following POUs participated:

State sector

ESTABLISHED PAEDIATRIC ONCOLOGY UNITS WITH ACCESS TO EXPERIENCED MULTIDISCIPLINARY CLINICAL TEAMS

1. Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg, Gauteng
2. Chris Hani Baragwanath Academic Hospital Johannesburg, Gauteng
3. Steve Biko Academic Hospital, Pretoria, Gauteng
4. Red Cross War Memorial Children's Hospital, Cape Town, Western Cape
5. Tygerberg Hospital, Cape Town, Western Cape
6. Universitas Hospital, Bloemfontein, Free State (private and public)
7. Inkosi Albert Luthuli Central Hospital, Durban, KwaZulu-Natal

NEWER PAEDIATRIC ONCOLOGY UNITS WITH RESTRICTED ACCESS TO EXPERIENCED MULTIDISCIPLINARY CLINICAL TEAMS

8. Polokwane Provincial Hospital, Polokwane, Limpopo
9. Dr George Mukhari Academic Hospital, Garankuwa
10. Frere Hospital, East London, Eastern Cape
11. Port Elizabeth Provincial Hospital, Port Elizabeth, Eastern Cape
12. Robert Mangaliso Sobukwe Hospital, Kimberley, Northern Cape
13. Greys Hospital, Pietermaritzburg, KwaZulu-Natal

PRIVATE HOSPITALS

14. Wits Donald Gordon Medical Centre, Johannesburg, Gauteng
15. Netcare Alberton Hospital, Johannesburg, Gauteng
16. Netcare Unitas Hospital, Pretoria, Gauteng
17. Lenmed eThekweni Hospital, Durban, KwaZulu-Natal

1.5.2 Process

The initial phase involved garnering commitment to collaborate from the South African paediatric oncology community. It was considered essential to document and analyse retrospective outcomes to inform the choice of regimens in the prospective study. Ongoing funding was obtained from various sources and in-person meetings were initiated. The team evaluated available literature and discussed retrospective outcomes from their centres to determine the treatment regimen suitable for the majority of POUs. Risk stratification based on grouping of Ann-Arbor staging was agreed upon by consensus to avoid undertreatment (see Appendices A and B). Table 1 demonstrates the comparison of the risk stratification schema adopted in this study with those of various other cooperative groups.

A pre-study assessment was conducted to ensure that all POUs met the minimum conditions to participate. Minimum criteria included availability of all the chemotherapy agents required in the treatment regimen, radiotherapy facilities and imaging capacity (see Appendix C).

The multidisciplinary team included paediatric oncologists, paediatric haematologists, radiation oncologists, a nuclear medicine physician and statisticians (computer science analysts and a health economist, all of whom had varying degrees of experience working with CRs on paediatric cancer studies). My role as PI included protocol creation, fundraising, coordination of communications, manuscript writing and submission for publication. I coordinated the creation of the treatment guideline and I grew into the role of content matter expert. A project WhatsApp group facilitated communication about study issues but was not used to discuss specific patients. Successive meetings were held (in-person and online) to discuss results of the retrospective study and fine-tune the prospective management algorithm. CRs were trained in the application of the prospective protocol and data capture on the REDCap database.

Within each POU, a designated CR champion was appointed with the responsibility of assimilating the knowledge and insights gained from the study and disseminating them to their respective local teams. The CR champion served as a key conduit for transferring the acquired information, ensuring its effective integration and implementation at each POU. Presentations were made available to ensure standardisation of radiological reporting, histopathological

diagnosis, radiation indication, fields and doses, and interim assessment by PET-CT. Once the COVID-19 pandemic started, the option of in-person meetings was no longer available and we continued with online meetings, and I made more regular phone calls and emails to individual CRs.

The management algorithm was piloted in the Johannesburg sites (CMJAH, CHBAH and WDGMC) and the data uploaded on the REDCap database to assess utility. The database was iteratively adapted to suit users and ensure data quality. Once the remaining individual POUs received Human Research Ethics Committee (HREC) approval, the study was initiated at each site and patients were enrolled on the study. Informed consent and assent was obtained from parents, guardians and patients and encompassed explicit permission for the use of anonymised data.

At the point where all POUs had started enrolling participants, I performed a mid-study assessment by engaging with all CRs. A simple questionnaire was devised (Appendix D) and after all the CRs had agreed to the process, I telephoned each CR individually to capture their responses. This approach was selected to address concerns in real-time, clarify any misunderstandings and maintain ongoing contact with all CRs.

Once data capture began, I assessed the quality of the data and interacted regularly with the CRs to facilitate quality control. Interim analyses were performed and communicated regularly with the CRs via online meetings. These were also an opportunity to discuss issues with the study protocol or management decisions for challenging cases. Particularly challenging cases were discussed with the content supervisor on email or in open fora to create learning opportunities for the CRs.

Resource constraints necessitated a creative approach to fundraising. Research grants from CANSA, the Carnegie Corporation Research Funding and the Faculty research Committee Individual Research Grant provided sufficient funds to launch the project and hire a research assistant for a short period, but ongoing funding was required and I turned to crowd-funding by riding the Ride Joburg 947 cycle race on three occasions. A series of temporary research coordinators assisted with the logistics of running regular meetings, regulatory requirements

and data collection in distant sites. Regulatory requirements included study approval in all POUs, registration on the National Health Research Database and the Provincial Health Research databases.

1.5.3 Study design

To inform the prospective study, we determined the baseline through a retrospective analysis to identify treatment regimens in use, determine efficacy in the South African setting and identify prognostic factors. These data were then used to inform the creation of a prospectively studied treatment regimen tailored to the local setting.

Important considerations included toxicity of the first-line regimen given the restricted access to antibiotics, blood products and intensive care; cost to the treating centre; availability of chemotherapy agents and access to radiotherapy and surgical skills. In-patient OEPA/OPPA-COPP was ruled out as procarbazine was available at the time only via application to the South African Health Products Regulatory Agency (SAHPRA) and many POUs had limited bed space for in-patient care. BEACOPP¹⁰⁵ and ABVE-PC¹⁰⁶ were deemed too toxic for the South African setting, ABVD was associated with good survival rates and acceptable toxicity in similar settings,¹⁰⁷ while COPDac was seen as acceptably intensified and avoided the use of the gonadotoxic procarbazine.^{57,108}

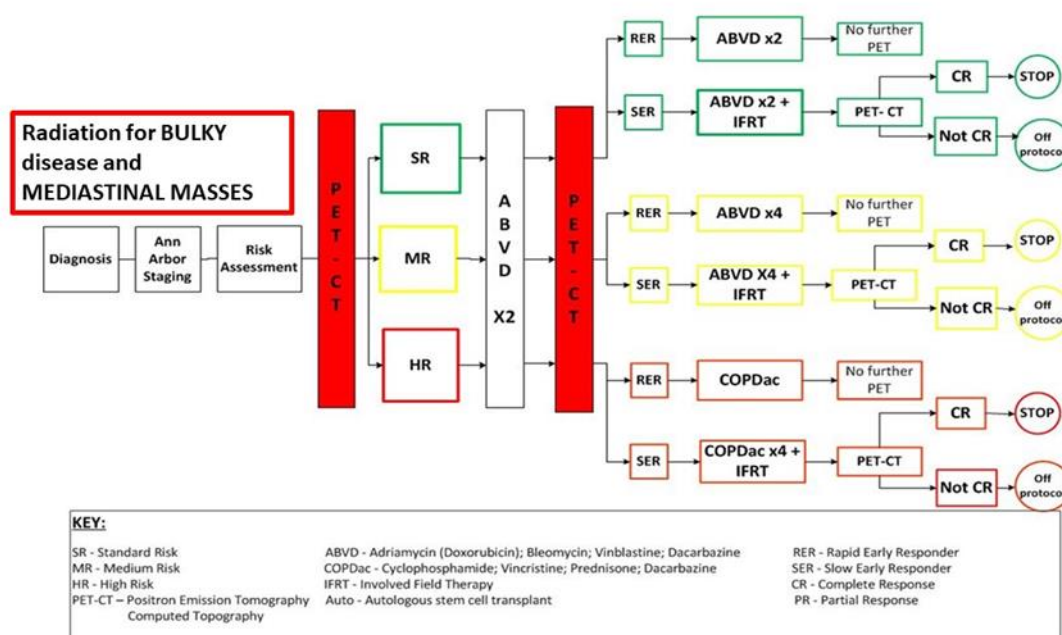


Figure 2. Treatment algorithm for patients on SACCSSG-HL-2018 study

The decision to utilise ABVD as the initial treatment modality in standard, medium, and high-risk patients was informed by the findings of the retrospective review. While some international groups do not recommend the use of ABVD as first-line therapy in high-risk paediatric patients,¹⁰⁹ evidence from similar settings demonstrated favourable efficacy.^{107,110} Additionally data from a large multicentre study demonstrated equivalent overall survival with no statistical difference in progression-free survival between ABVD and escalated BEACOPP, with higher rates of toxicity in patients treated with eBEACOPP.¹¹¹ This decision was made with the knowledge that effective salvage options were available within the South African context. These include certain second-line therapies and autologous stem cell transplantation in a limited number of state and private POUs.¹¹² Furthermore, the extensive historical utilisation of ABVD as a standalone therapy over several decades contributed to the confidence in its effectiveness.^{14,68,107,113–116}

The decision to include radiotherapy for mediastinal masses was based on various studies which documented efficacy with limited radiation fields to minimise toxicity to the heart and lungs.^{39,107} The recommended radiotherapy dosage was 21-25 Gy, lower than the dose used in adult studies, to decrease the possibility of long-term adverse effects such as breast cancer and cardiotoxicity. Radiotherapy units that could offer more limited fields such as 3D conformal

involved node rather than involved field radiation were encouraged to do so, and larger fields such as mantle and inverted Y fields were discouraged (see Figure 1).

There was no experimental arm, and all treatment was considered standard of care. However, the distinguishing factor lay in the establishment of a consensus regarding diagnosis, risk stratification, interim assessment and the subsequent implementation of treatment consolidation or intensification.

1.5.4 Participants

Patients recruited to the study included those with newly diagnosed, previously untreated cHL, which excluded nodular lymphocyte predominant cHL. We included all patients under 19 years old, as certain POUs were able to treat patients up to the age of 19. Patients who could not receive doxorubicin due to prior cardiac dysfunction were treated with COPDac instead of ABVD. For the feasibility part of the study (Chapter 4), the CRs themselves were participants.

1.5.5 Data capture and data management

Each POU had a dedicated CR who was trained to follow the treatment guideline and enter data into the central REDCap database, located on the University of the Witwatersrand servers. The data was regularly assessed and follow-up given to the CRs via email, WhatsApp messages and telephone calls. CRs who were unable to enter data sent digital copies of the patient notes to be captured and site visits were performed to capture missing data.

1.5.6 Statistical methods

Simple descriptive statistics were utilised for patient characteristics with mean and standard deviation for normally distributed data, and median with range for non-parametric data. Frequency tables were generated for categorical variables. Summary measures were provided for continuous variables using mean with standard deviation if data were normally distributed, otherwise, the median with range was reported. Differences between independent groups were analysed using Mann-Whitney U-test, Chi-square and Student t-test. Overall descriptive survival was evaluated using Kaplan–Meier analysis. OS was defined from the date of diagnosis

until the date of death or date last seen. Event-free survival (EFS) was calculated from date of diagnosis until disease progression, the last recorded date if the patient abandoned therapy or the date of death. EFS served as the metric for the retrospective study to include all events, as the retrospective data was less structured than the prospective data and not all patients had precisely documented dates of progression. In the prospective study, progression-free survival (PFS) was calculated from the date of diagnosis until disease progression or death.

The prospective study accrued 165 patients, of whom 132 were analysed for the publications as they had been on study for the required duration. The remainder have not yet completed treatment and are thus not eligible for analysis here. Kaplan-Meier survival curves were generated to calculate survival probabilities, with Cox regression to determine the significance of individual prognostic factors. Conventional statistical significance was set at $p \leq 0.05$.

In order to assess the relative significance of changes in blood markers compared to interim PET-CT findings (Chapter 6), receiver operating characteristic (ROC) curves were generated. This analytical approach allows for the evaluation of classification models across various threshold settings by plotting true positive rates against true negative rates, ultimately yielding an area under the curve (AUC). The AUC values range from 0.0 to 1.0, with values closer to 1.0 indicating higher sensitivity and specificity¹¹⁷. An AUC value of 0.5 suggests random chance prediction accuracy, while a value of 1.0 signifies perfect prediction accuracy. The use of AUC is advantageous for two reasons: AUC is scale-invariant, i.e. it assesses the ranking of predictions rather than their absolute values. Secondly, AUC is classification-threshold-invariant, indicating that it measures the predictive quality of the model regardless of the chosen classification threshold. Various machine learning models were used to determine the best fit, including logistic regression, Random Forests, naïve Bayes and support vector machine classifiers. More detailed explanations follow in each chapter.

1.5.7 Ethics and regulatory requirements

The retrospective and prospective studies were separately approved by the Wits HREC (see Appendices E and F). The prospective study was additionally approved by the HRECs of each individual POU and registered on the national health research database (NHRD) as well as the provincial health research databases of each POU. The consent and assent forms (see

Appendices G and H) were made available in English, Afrikaans, isiZulu, Setswana and Northern Sotho according to the requirements of the different ethics committees.

As the prospective study did not include experimental therapies or novel approaches, there was no anticipation of excess harm to participants except for the potential of data breach. The REDCap database is hosted on two separate secure servers on the Wits campuses with firewalls, access controls and appropriate encryption. Parents/guardians and patients gave informed consent and assent for their data to be used in anonymised analyses and anonymised data analysis was performed on password-protected computers.

Chapter 2. cHL OS in South Africa 2000-2010

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RESEARCH ARTICLE

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

Jennifer A. Geel¹ | Tobias C. Chirwa² | Biance Rowe³ | Katherine C. Eyal⁴ |
Fareed Omar⁵ | David K. Stones⁶ | Yasmin Goga⁷ | D. Cristina Stefan⁸ | Anel van
Zyl⁹ | Barry Van Emmenes¹⁰ | Oloko Wedi¹¹ | Manickavallie Vaithilingum¹² |
Marc G. Hendricks¹³ | for the South African Children's Cancer Study Group

¹Faculty of Health Sciences, University of the Witwatersrand, Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg, South Africa

²Division of Epidemiology and Biostatistics, School of Public Health, University of the Witwatersrand, Johannesburg, South Africa

³Faculty of Health Sciences, University of the Witwatersrand, Chris Hani Baragwanath Academic Hospital, Johannesburg, South Africa

⁴Faculty of Economics, University of Cape Town, Cape Town, South Africa

⁵Faculty of Health Sciences, University of Pretoria, Steve Biko Academic Hospital, Pretoria, South Africa

⁶Faculty of Health Sciences, University of the Free State, Universitas Hospital, Bloemfontein, South Africa

⁷Faculty of Health Sciences, University of Kwazulu-Natal, Inkosi Albert Luthuli Hospital, Durban, South Africa

⁸South African Medical Research Council, Parow, South Africa

⁹Faculty of Health Sciences, University of Stellenbosch, Tygerberg Hospital, Tygerberg, South Africa

¹⁰Division of Paediatric Haematology and Oncology, Frere Hospital, East London, South Africa

¹¹Division of Paediatric Haematology and Oncology, Polokwane-Mankweng Hospital Complex, Polokwane, South Africa

¹²Netcare Parklands Hospital, Durban, South Africa

¹³Faculty of Health Sciences, University of Cape Town, Red Cross War Memorial Children's Hospital, Cape Town, South Africa

Correspondence

Jennifer A. Geel, Ward 294, Division of Paediatric Haematology and Oncology, Charlotte Maxeke Johannesburg Academic Hospital, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, Gauteng 2000, South Africa.
Email: jennifer.geel@wits.ac.za

Abstract

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

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

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

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

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

KEYWORDS

Hodgkin disease, prognostic indicators, SACCSG, South Africa

1 | INTRODUCTION

Survival rates of children with Hodgkin lymphoma (HL) in excess of 90% are well documented in high-income countries (HICs).¹ South Africa is an upper middle income country of 54 million people² with a healthcare system based on both state and private funding. Gross inequalities between the public and private healthcare sectors have persisted and in places widened since 1994, with the inception of democracy in South Africa. The public healthcare sector is heavily subsidised from the national fiscus, while the private healthcare sector is funded by the individuals receiving health care and medical insurers. Inequitable access to health care, financial constraints, limited follow-up, co-morbid disease (particularly tuberculosis, human immunodeficiency virus [HIV] and chronic malnutrition) continue to challenge effective healthcare delivery in South Africa.³ In addition, maladministration has contributed to disparities in healthcare provision across different provinces in the country.⁴ The burden of HIV disease grew in the period 1994 to the present and has only recently started to diminish with the widespread availability of state-funded antiretroviral (ARV) medication since 2003.^{5,6} HL has established itself as an HIV-related malignancy in the adult HIV-infected population,⁷ but a similar trend has not been identified in the paediatric population in African studies.^{8–10}

Challenges to childhood cancer treatment in low- and middle-income countries (LMICs) include limited or erratic access to chemotherapy, radiotherapy and specialised services.¹¹ Various approaches to treatment of HL have been applied, including regimens that include¹² or exclude¹³ radiotherapy in equivalent socio-economic settings with satisfactory results. In South Africa, patients have been treated on a variety of hybrid or single-arm protocols with or without radiotherapy, according to institutional preference.

The South African Children's Cancer Study Group (SACCSG) was founded in 1987 to coordinate paediatric cancer care at various sites. Political and economic challenges have resulted in the group assuming an advocacy role for many years, but the focus has recently shifted

from one of service delivery to multi-centre cooperation and dissemination of research findings in an effort to improve survival rates. In October 2013, the organisation undertook to report its national HL data from both the public and private health sectors. This article represents the cumulative efforts of all dedicated paediatric oncology units (POUs) in the country to determine survival rates and prognostic factors in a South African population. This report is a retrospective review of all children with HL diagnosed and treated in South Africa between 2000 and 2010.

2 | MATERIALS AND METHODS

2.1 | Patient population

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

2.2 | Staging and imaging

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

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

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

2.3 | Treatment

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

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

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

2.4 | Statistical analysis

Data were entered into a central, anonymised database managed by a single researcher. Descriptive statistics were presented. For categorical variables such as sex, ethnic group and HIV status, frequency tables were presented. For continuous variables such as age, summary measures were presented using mean with standard deviation if data were normally distributed, otherwise the median with range was reported. Other variables included histological subtype, stage, treatment regimen, treatment site, toxicity rates and causes of death. Potential

differences between independent groups were elucidated using Student *t*-test or Mann–Whitney *U* test. Overall descriptive survival was evaluated using Kaplan–Meier analysis. Overall survival (OS) was defined from the date of diagnosis until the date of death or date last seen. Event-free survival was calculated from date of diagnosis until disease progression or death. Treatment failure was calculated from the date of diagnosis until the date of progression of disease, relapse or death from any cause. Refractory disease was diagnosed in those patients who failed to obtain a complete response with initial therapy or those who relapsed within 3 months from the end of initial therapy. Late relapse was defined as relapse more than 6 months from the completion of therapy. Treatment abandonment was defined as failure to initiate or complete treatment with a curative intent, except when the treating physician elected to stop treatment. Loss to follow-up was defined as any patient who did not return for follow-up appointments for 1 year and was unreachable despite efforts to contact the family. These patients were censored in the survival curves. To assess the statistical significance of various prognostic factors, univariate and multiple Cox regression modelling technique was used with death defined as an end point. All factors found significant at 20% level in the univariate level were considered for adjustment in the multiple regression models. For all other calculations, a *P* value of less than 0.05 was considered significant. Permission to conduct retrospective analyses was obtained from the relevant human research ethics committees at individual study sites. The cut-off for data analysis was October 2015.

3 | RESULTS

In total, 301 cases of HL were reported from January 2000 to December 2010, representing 3.7% of the total number of reported malignancies in South African children during this interval.¹⁸ The reported age-standardised ratio during this period was 2.2 per million.¹⁸ The demographic data and disease characteristics on presentation are shown in Table 1. Data from six patients were excluded, as they were treated elsewhere, and one patient was found not to have HL at review of histology. The incidence of HL increased with age and a male predominance (sex ratio of 3.3:1) was shown. The majority of the patients were of African ancestry (217), followed by 43 of mixed ancestry, 22 of Caucasian and 12 of Indian descent. The median age was 9.6 years (range 2.9–18.8 years), with no significant difference in ages linked to ethnicity. The majority of patients (63.6%) were younger than 11 years of age, although it must be noted that individual institutional policies dictated that certain units treat patients up to the age of 12 years, some to 15 years and some to 18 years. Male patients were significantly younger than female patients, with a median of 9.3 years versus 11 years in females (*P* = 0.0158). Twenty-nine (9.9%) of the patients were HIV positive (Table 1). Only 9 of the 29 HIV-positive patients were on ARV therapy at the time of diagnosis of HL, and 7 of these had undetectable HIV viral loads. Data on the duration of ARV treatment prior to presentation were not included in this study. The national roll-out of state-funded ARV therapy started in November 2003⁶ and thus

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

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

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

The majority of patients presented with Stage III and IV disease (55.4%) and B symptoms (59.2%). Children with HIV presented with more late stage disease (23/29, 79%) than their HIV-negative counterparts (135/254 53%, $P = 0.002$). There was no correlation between ethnicity and late presentation (Student t -test, $P = 0.45$, correlation coefficient 0.0443). Patients with Stage IV disease ($n = 80$) included 25 with bone marrow involvement, 6 with bone involvement, 3 with liver involvement, 32 with a combination of bone, bone marrow and liver and 14 with other sites including parenchymal lung disease. Twenty-seven patients (9.5%) presented with autoimmune manifestations which included immune thrombocytopenic purpura (ITP) in

4 patients, nephrotic syndrome in 4 and autoimmune haemolytic anaemia (AIHA) in 10 patients, the combination of AIHA and ITP in 5 patients and rheumatoid arthritis in 4 patients. In addition, one patient presented with secondary haemophagocytic lymphohistiocytosis. Bulky disease was present in 38.8% of the patients. Histological subtypes are represented in Table 1. Only 153/294 (52%) specimens were tested for Epstein-Barr virus latent membrane protein (LMP) expression and 22 (14.4%) of these demonstrated LMP expression.

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

3.1 | Imaging

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

3.2 | Management protocols

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

3.3 | Haemopoietic stem cell transplants

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

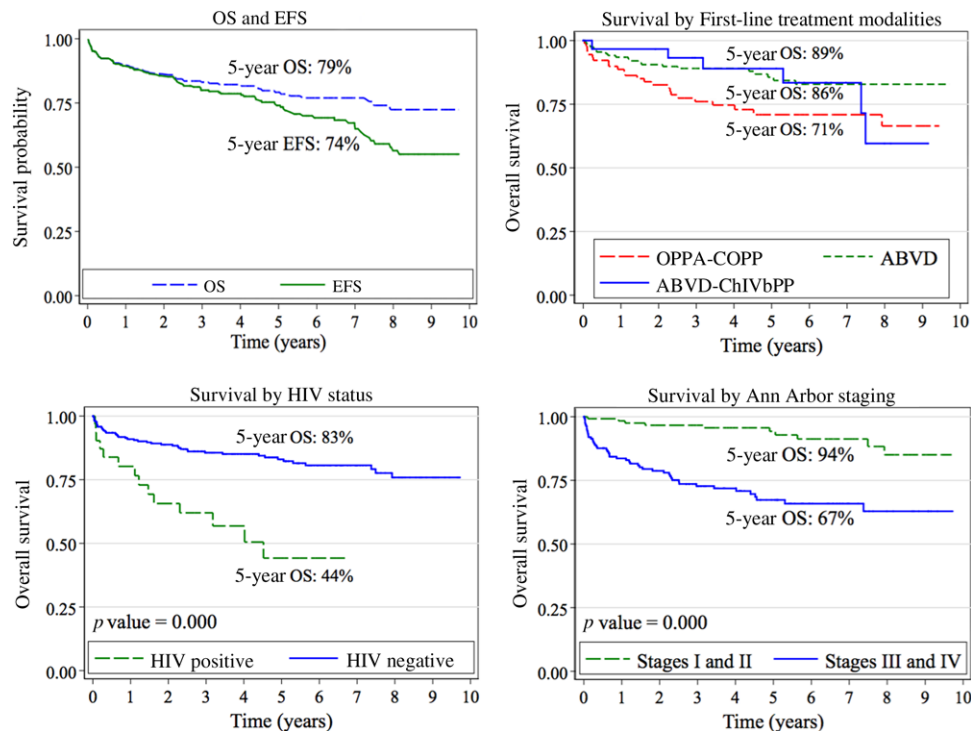


FIGURE 1 Kaplan–Meier survival curves of patients treated for HL in South Africa

3.4 | Overall survival

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

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

3.5 | Poor prognostic factors

These results demonstrated that children older than 10 years (75.9 vs. 82.2%) with HIV infection (44.2 vs. 83.0%) and Stage III and IV disease

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

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

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

3.6 | Follow-up

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

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

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

^aNo deaths recorded.

Ref denotes the reference value against which other values were compared.

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

4 | DISCUSSION

This study marks a landmark in the history of the SACCSG, as it is the first report of South African oncology patients in which all POU contributed data. More than half the patients in this study presented with Stage III and IV disease, in keeping with reports from other LMICs.^{19–22} The OS rate compares favourably with that in other upper middle

income countries, but there are numerous opportunities for improvement.

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

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

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

^aNo deaths recorded.

Ref denotes the reference value against which other values were compared.

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

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

The Type 1 epidemiological pattern, comprising mainly mixed cellularity and lymphocyte-depleted subtypes, is said to be characteristic of low-income countries. The Type 3 pattern, noted in HICs, is characterised by mainly nodular sclerosing subtype and less marked male predominance.²⁵ South African children with HL appear to fall into a Type 2 pattern, as found in a “developing” country^{26,27} based on

the marked male predominance, equal proportions of mixed cellularity and nodular sclerosing subtypes and majority presentation in the first decade of life. It is possible that varying upper age limits for admission to South African POUs may have skewed the data towards the younger age groups. Previous reports have demonstrated the striking relationship between socio-economic and environmental factors and affected age groups,^{25,26,28} stating that an increased proportion of younger children with HL is found in countries with poor socio-economic conditions.

The HIV incidence rate of 9.9% in this cohort parallels the rate of HIV infection in the country during this period,² reflecting the findings of three South African studies^{8,10,29} and a Malawian study⁹ which did not confirm an increased incidence of HL in an HIV-positive paediatric population. ARV therapy became available to affected children in 2003⁶ and thus the outcome of some of these patients may have been affected by the lack of access to definitive treatment.

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

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

The 5-year OS rate of 79% is encouraging for a middle-income country with a fragmented healthcare system. The refinement of imaging and supportive treatment modalities over time has undoubtedly contributed to lower relapse rates in this group of patients. The priority for South African paediatric haemato-oncologists is to improve survival rates while limiting toxicities. Not all South African POUs are well equipped to deal with severe treatment-related toxicities: as an example, most hospitals have very limited intensive care facilities³⁵ which often cannot accommodate patients with malignancy-related complications. With stem cell transplant only available in three state-funded institutions, and newer agents as yet unregistered for use in South Africa, access to more sophisticated salvage therapy options is limited. Issues such as chemotherapy-induced infertility are generally not considered priorities by health regulators in middle-income countries such as South Africa and it thus behoves clinicians to highlight these issues in long-term healthcare planning for children with cancer. The findings of this study may be of benefit for clinicians in other LMICs, where the majority of children with cancer are treated.

5 | CONCLUSIONS AND RECOMMENDATIONS

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

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

REFERENCES

- Smith MA, Seibel NL, Altekruse SF, et al. Outcomes for children and adolescents with cancer: challenges for the twenty-first century. *J Clin Oncol*. 2010;28(15):2625–2634.
- Statistics South Africa. Statistical release P0302. Mid-year population estimates 2014. Available from: <http://www.statssa.gov.za/publications/P0302/P03022014.pdf>.
- Stuckler D, Basu S, McKee M. Health care capacity and allocations among South Africa's provinces: infrastructure-inequality traps after the end of apartheid. *Am J Public Health*. 2011;101(1):165–172.
- Rispel LC, de Jager P, Fonn S. Exploring corruption in the South African health sector. *Health Policy Plan*. 2016;31(2):239–249. doi:10.1093/heapol/czv047
- HIV and AIDS in South Africa. AVERT. Last updated 09 January 2017. Accessed 09 March 2017. Available from <https://www.avert.org/professionals/hiv-around-world/sub-saharan-africa/south-africa>
- Johnson LF. Access to antiretroviral treatment in South Africa, 2004–2011. *Southern African Journal of HIV Medicine*, North America, March 13, 2012. <http://www.sajhivmed.org.za/index.php/hivmed/article/view/156/261>.
- Stein L, Urban ML, O'Connell D, et al. The spectrum of human immunodeficiency virus-associated cancers in a South African black population: results from a case-control study, 1995–2004. *Int J Cancer*. 2008;122:2260–2265.
- Davidson A, Wainwright RD, Stones DK, et al. Malignancies in South African children with HIV. *J Pediatr Hematol Oncol*. 2014;36(2):111–117.
- Mutalima N, Molyneux EM, Johnston WT, et al. Impact of infection with human immunodeficiency virus-1 (HIV) on the risk of cancer among children in Malawi—preliminary findings. *Infect Agent Cancer*. 2010;5:5. doi:10.1186/1750-9378-5-5
- Bohlius J, Maxwell N, Spoerri A, et al. Incidence of AIDS-defining and other cancers in HIV-positive children in South Africa: record linkage study. *Pediatr Infect Dis J*. 2016;35(6):e164–e170.
- Kruger M, Hendricks M, Davidson A, et al. Childhood cancer in Africa. *Pediatr Blood Cancer*. 2014;61(4):587–592. doi:10.1002/pbc.24845
- Sackmann-Muriel F, Zubizarreta P, Gallo G, et al. Hodgkin disease in children: results of a prospective randomized trial in a single institution in Argentina. *Med Pediatr Oncol*. 1997;29:544–552.
- Al-Tonbary Y, Sarhan MM, El-Ashry R, Fouda A. Comparative study of two-mechlorethamine, vincristine, procarbazine and prednisone derived chemotherapy protocols for the management of pediatric Hodgkin lymphoma: single-center 5-year experience. *Leuk Lymph*. 2010;51(4):656–663.
- Carbone PP, Kaplan HS, Musshoff K, Smithers DW, Tubiana M. Report of the committee on Hodgkin's disease staging classification. *Cancer Res*. 1971;31:1860–1861.
- Bonadonna G, Viviani S, Bonfante V, Gianni AM, Valagussa P. Survival in Hodgkin's disease patients—report of 25 years of experience at the Milan Cancer institute. *Eur J Cancer*. 2005;41(7):998–1006.
- Dieckmann K, Pötter R, Wagner W, Prott FJ, Schellong G. Stage adapted combination therapy with OPPA (or OEPA)/COPP chemotherapy and low-dose radiotherapy in children and adolescents with Hodgkin's disease. Results of the German/Austrian Pediatric Therapy Study DAL-HD-90 in 578 patients. *J Clin Oncol*. 2010;28(23):3680–3686. doi:10.1200/JCO.2009.26.9381
- Shankar A, Visaduraki M, Hayward J, Morland B, McCarthy K, Hewitt M. Clinical outcome in children and adolescents with Hodgkin lymphoma after treatment with chemotherapy alone—the results of the United Kingdom HD3 national cohort trial. *Eur J Cancer*. 2012;48:108–113.
- Stefan DC, Stones DK, Wainwright D, et al. Childhood cancer incidence in South Africa, 1987–2007. *S Afr Med J*. 2015;105(11):939–947.
- Jacobs P, King H, Karabus C, Hartley P, Werner D. Hodgkin's disease in children: a ten-year experience in South Africa. *Cancer*. 1984;53:210–213.

20. Hesselting PB, Wessel G, van Jaarsveld D, van Riet FA. Hodgkin's disease in children in Southern Africa: epidemiological characteristics, morbidity and long-term outcome. *Ann Trop Paediatr*. 1997;17:367–373.
21. Cohen C, Hamilton DG. Epidemiologic and histologic patterns of Hodgkin's disease: comparison of the black and white populations of Johannesburg, South Africa. *Cancer*. 1980;46(1):186–189.
22. Sherief LM, Elsafy UR, Abdelkhalek ER, et al. Hodgkin Lymphoma in childhood. Clinicopathological features and therapy outcome at 2 centers from a developing country. *Medicine (Baltimore)*. 2015;94(15):e670.
23. Lee C. "Race" and "ethnicity" in biomedical research: how do scientists construct and explain differences in health? *Soc Sci Med*. 2009;68(6):1183–1190. doi:10.1016/j.socscimed.2008.12.036
24. Stefan DC, Stones D, Dippenaar A, Kidd M. Ethnicity and characteristics of Hodgkin lymphoma in children. *Pediatr Blood Cancer*. 2009;52(2):182–185. doi:10.1002/pbc.21804
25. Correa P, O'Connor GT. Epidemiological patterns of Hodgkin's disease. *Int J Cancer*. 1971;8:192–201.
26. Cavdar AO, Pamir A, Gözdaşoglu S, et al. Hodgkin disease in children: clinicoepidemiologic and viral (Epstein–Barr virus) analyses. *Med Pediatr Oncol*. 1999;32(1):18–24.
27. Dinand V, Arya LS. Epidemiology of childhood Hodgkin's disease: is it different in developing countries? *Ind Pediatr*. 2006;43:141–147.
28. Jacobson RJ, Klappenbach RS, Clinton C, de Moor NG, Wong O. Hodgkin's disease in South African Children. *S Afr Med J*. 1981;59(5):133–137.
29. Stefan DC, Wessels G, Poole J, et al. Infection with human immunodeficiency virus-1 (HIV) among children with cancer in South Africa. *Pediatr Blood Cancer*. 2011;56(1):77–79. doi:10.1002/pbc.22672
30. Váróczy L, Gergely L, Zeher M, Szegedi G, Illés A. Malignant lymphoma-associated autoimmune diseases—a descriptive epidemiological study. *Rheumatol Int*. 2002;22:233–237. doi:10.1007/s00296-002-0229-4
31. Moncharmont P, Ghesquieres H, Sebban C, et al. Severe IgA-mediated autoimmune haemolytic anaemia in Hodgkin lymphoma: a very rare event. *Leuk Lymphoma*. 2007;48(3):633–635. doi:10.1080/10428190601120357
32. Jerónimo M, Silva S, Benedito M, Brito MJ. Hodgkin's lymphoma and autoimmunity: is there a relationship? *Acta Med Port*. 2015;28(6):749–753.
33. Hessissen L, Khtar R, Madani A, et al. Improving the prognosis of pediatric Hodgkin lymphoma in developing countries: a Moroccan Society of Pediatric Hematology and Oncology study. *Pediatr Blood Cancer*. 2013;60:1464–1469.
34. Castellanos EM, Barrantes JC, Báez LF, et al. A chemotherapy only therapeutic approach to pediatric Hodgkin lymphoma: AHOPCA LH 1999. *Pediatr Blood Cancer*. 2014;61(6):997–1002. doi:10.1002/pbc.24905
35. Argent AC, Ahrens J, Morrow BM, et al. Pediatric intensive care in South Africa: an account of making optimum use of limited resources at the Red Cross War Memorial Children's Hospital. *Pediatr Crit Care Med*. 2014;15(1):7–14.

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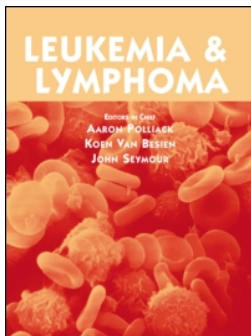
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ORIGINAL ARTICLE



Prognostic factors affecting survival in children and adolescents with HIV and Hodgkin lymphoma in South Africa

Jennifer Ann Geel^a , Katherine Claire Eyal^b , Marc Gerald Hendricks^c , Khumo Hope Myezo^a , David Kenneth Stones^d , Fareed Omar^e , Yasmin Goga^f , Anel van Zyl^g , Barry van Emmenes^h , Manickavallie Vaithilingumⁱ , Shaegan Irusen^j , Rossella Marina Bandini^j , Oloko Wedi^k , Bianca Rowe^l , Daynia Elizabeth Ballot^j , and Monika L. Metzger^m  and For the South African Children's Cancer Study Group

^aDivision of Paediatric Haematology/Oncology, Faculty of Health Sciences, University of the Witwatersrand, Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg, South Africa; ^bFaculty of Economics, University of Cape Town, Cape Town, South Africa; ^cDivision of Paediatric Haematology/Oncology, Faculty of Health Sciences, University of Cape Town, Red Cross War Memorial Children's Hospital, Cape Town, South Africa; ^dDivision of Paediatric Haematology/Oncology, Faculty of Health Sciences, University of the Free State, Universitas Hospital, Bloemfontein, South Africa; ^eDivision of Paediatric Haematology/Oncology, Faculty of Health Sciences, University of Pretoria, Steve Biko Academic Hospital, Pretoria, South Africa; ^fDivision of Paediatric Haematology/Oncology, Faculty of Health Sciences, University of Kwazulu-Natal, Inkosi Albert Luthuli Central Hospital, Durban, South Africa; ^gDivision of Paediatric Haematology/Oncology, Faculty of Health Sciences, University of Stellenbosch, Tygerberg Hospital, Cape Town, South Africa; ^hDivision of Paediatric Haematology/Oncology, Walter Sisulu University, Frere Hospital, East London, South Africa; ⁱNetcare Parklands Hospital, Durban, South Africa; ^jFaculty of Health Sciences, University of the Witwatersrand, Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg, South Africa; ^kDivision of Paediatric Haematology/Oncology, University of Limpopo, Polokwane-Mankweng Hospital Complex, Polokwane, South Africa; ^lFaculty of Health Sciences, University of the Witwatersrand, Chris Hani Baragwanath Academic Hospital, Soweto, South Africa; ^mSt Jude Children's Research Hospital, University of Tennessee Health Sciences Center, Memphis, TN, USA

ABSTRACT

South African children with Hodgkin lymphoma (HL) and human immunodeficiency virus (HIV) have low 5-year overall survival (OS) rates. In this retrospective multicenter study, 271 South African pediatric patients with HL were studied to determine OS and prognostic factors in those with HIV and HL. Univariate risk factor analysis was performed to analyze prognostic factors. The 29 HIV-infected patients were younger ($p = .021$), more likely to present with wasting (0.0573), stunting (0.0332), and Stage IV disease ($p = .000$) than HIV-uninfected patients. The 5- and 10-year OS of HIV-infected patients of 49% and 45% versus 84% and 79%, respectively for HIV-uninfected patients ($p = .0001$) appeared to be associated with hypoalbuminemia (<20 g/dL) and CD4 percentage of $<15\%$. Causes of death in the HIV-infected group included disease progression (6/14), infection (4/14), unknown (3/14), and second malignancy (1/14). HIV-infected pediatric patients with HL experience increased mortality due to post-therapy opportunistic and nosocomial infections.

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Introduction

Hodgkin lymphoma (HL) and human immunodeficiency virus (HIV) are immune disorders which, when occurring in tandem in children with immature immune systems, can have devastating consequences. HL is associated with immune dysregulation [1] and HIV infection results in losses of both cellular and humoral immunity [2,3].

South Africa is home to the world's largest cohort of people living with HIV, with an estimated 7,700,000 people living with HIV in 2018, 260,000 of them children under 14 years [4]. The HIV epidemic has had a profound impact on childhood mortality and socio-economic conditions in Africa [5–7]. Steady improvements have been made in increasing access to antiretroviral therapy (ART) resulting in an increased lifespan of children with HIV [4,8,9]. While HL has

CONTACT Jennifer Ann Geel  jennifer.geel@wits.ac.za  Ward 294, Division of Paediatric Haematology and Oncology, Charlotte Maxeke Johannesburg Academic Hospital, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, 2000, Gauteng, South Africa
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been associated with HIV in adults, it is not considered an AIDS-defining cancer, and a similar trend has not been conclusively shown in children and adolescents [10–12].

Limited studies report an increased mortality risk for patients with both HIV and various cancers due to infections [13,14] but there is no published data on pediatric HIV and HL. A retrospective, multicenter study identified that HIV-infected children in South Africa who develop HL have a significantly lower 5-year overall survival (OS) rate than their HIV uninfected counterparts [14]. The aim of this study was to identify risk factors associated with inferior survival rates between these HIV-infected and -uninfected children and adolescents and to determine long-term OS.

Materials and methods

The setting

South Africa is an upper-middle-income country which had ten pediatric oncology units (POUs) at the time of the retrospective study. The majority of children and adolescents with both HL and HIV were treated in state hospitals where care was largely subsidized, with free care for all children less than 6 years. ART was available free-of-charge in state facilities.

Patient population

Data were drawn from the ten participating centers for the period 1 January 2000–31 December 2010 and included all treatment-naïve, histologically confirmed cases of HL in children and adolescents (less than 18 years). Exclusion criteria included patients who were treated at other centers after diagnosis, and those in whom the HIV status was undocumented. Patients from both the private and the public sectors were treated with the same treatment protocols.

Ethics

Permission to conduct retrospective analyses was obtained from the human research ethics committee of the University of the Witwatersrand (clearance certificate number M1711100).

Histopathology

Pathology specimens were processed at the National Health Laboratory Services at the participating centers and reviewed by a single pathologist.

Staging of HL

Staging procedures have previously been described and consisted mainly of computerized tomography scans and chest X-rays [14]. Early-stage disease was defined as Stages I and II, while late-stage disease was defined as Stages III and IV. Bulky disease was defined as lymph nodes or lymph node aggregates greater than 6 cm in the long axis, or mediastinal adenopathy $\geq 33\%$ of the thoracic diameter [15].

Treatment

Patients were treated according to institutional preference with vincristine, procarbazine/etoposide, prednisone, adriamycin-cyclophosphamide, vincristine, prednisone, procarbazine (OPPA/OEPA-COPP), adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD), or ABVD-chlorambucil, vinblastine, procarbazine, prednisolone (ABVD-ChIVVP). Patients receiving OPPA/OEPA-COPP received involved-field radiotherapy (median 25 Gy) as a matter of course, while those receiving other regimens received radiation for residual or bulky disease only according to treating physicians' preference.

Interim assessments were not routinely performed in all centers but were done if there was clinical suspicion of lack of response to chemotherapy. HIV-infected patients were treated with the same chemotherapy protocols as uninfected patients. Dose modifications and administration of granulocyte-colony stimulating factor (G-CSF) were used in selected patients regardless of HIV status at the discretion of the treating clinicians. According to national policy at the time, cotrimoxazole prophylaxis was given to all HIV-infected patients with AIDS-defining CD4 counts, while prophylactic fluconazole was given at the discretion of the treating clinician. Cotrimoxazole was not given routinely to HIV-uninfected patients as *Pneumocystis jirovecii* was not commonly seen in this population. HIV therapy was freely provided to all HIV-infected patients in the public sector from 2003 onwards: this consisted of azidothymidine (AZT), stavudine, and lopinavir + ritonavir/efavirenz. Patients were screened for tuberculosis if there was clinical suspicion and treated if infected.

HIV infection characteristics

HIV infection was diagnosed by ELISA in all patients, either before presentation with their oncological diagnosis, or concurrently in those whose HIV diagnosis was made when they presented with HL. HIV viral loads were measured by polymerase chain reaction.

Further documentation included whether patients were on ART at the time of diagnosis with HIV, and whether they had achieved viral suppression defined as an undetectable viral load. Immunological stage data of HIV disease was not available for any of the patients.

Nutritional parameters

Height, weight, body mass index (BMI), and albumin level were recorded. Nutritional parameters were defined according to WHO definitions: obese/overweight, adequate, or BMI <2 standard deviations (2SD) according to standardized tables for age and sex. Wasting was defined as weight-for-age <2 SD and stunting was defined as height-for-age <2 SD. Weight-for-height tables were not used as the WHO recommends these for the age group 2–5 years, and the majority of patients in this study fell out of this age range.

Statistical analysis

This study analyzes a subset of HIV-infected patients from a previously published report which found that HIV-infected children had a significantly lower survival rate, but did not elucidate the reasons for this finding.

Demographic data included age, sex, nutritional parameters as defined above, HIV status with CD4 percentage and HIV viral load for HIV-infected patients. Other variables included histological subtype, stage, autoimmune manifestations of HL (nephrotic syndrome, hemolytic anemia, and immune thrombocytopenic purpura), treatment regimen, treatment site, last follow-up date (date last seen alive or date of abandonment of treatment), survival status, and cause of death. Baseline characteristics were summarized using descriptive statistics. The characteristics and outcomes of HIV-infected patients were compared to the group of uninfected patients. Odds ratio with Pearson's chi-square test was applied to categorical data to determine if differences between groups were statistically significant. Statistical significance was defined as a p value $<.05$.

Primary refractory disease was diagnosed in those with progression during treatment or up to 3 months from end of treatment. Treatment abandonment was defined as failure to complete curative treatment, or failure to appear for scheduled therapy for more than 4 weeks, except when patients were managed palliatively and these patients were censored at the time of abandonment. Loss to follow-up was defined as failure

to return for follow-up appointments for more than 1 year after successful completion of therapy. These patients were censored in the survival curves.

OS was defined from the date of diagnosis until death or date last seen alive and included patients not treated with curative intent. Five- and ten-year OS rates were calculated using Kaplan–Meier analysis with log-rank Cox regression modeling to assess survival differences between groups (parameters included age, sex, nutritional parameters, B symptoms, stage, bulky disease, histological subtype, CD4 percentage, treatment site, and chemotherapy regimen) with unadjusted hazard ratios for OS. Radiotherapy was not considered in this analysis as it was inconsistently administered. The cutoff for data analysis was 1 January 2020 to obtain data on 10-year survival rates.

Results

Between January 2000 and December 2010, 299 cases of pediatric HL patients were identified, of which 28 were excluded because they were treated elsewhere (8), had an unknown HIV status (14) or refused treatment upfront (6) (see [Figure 1](#)). Of the 271 eligible patients, 29 (10.7%) were HIV-infected (see [Figure 1](#)). The median age of HIV-infected patients was 7.2 years (range 3.3–16.3 years), in comparison with a median of 10 years (range 2.9–18.8 years) in the HIV-uninfected patients ($p = .021$), with a male predominance in both groups (3.4:1 in both). Although there were no specific policies precluding treatment of children with HIV, one POU reported no children with HIV in their dataset.

The majority (17/29, 76%) of HIV-infected children presented with late-stage disease, while 132/242 (55%) HIV-uninfected children presented with late-stage disease ($p = .015$) (see [Table 1](#)). There were no significant differences in BMI between the two groups, but HIV-infected patients exhibited more wasting, stunting, and hypoalbuminemia. HIV-infected patients were more likely to present with autoimmune manifestations of HL but the trend was not significant ($p = .117$) (see [Table 1](#)).

Of the 29 HIV-infected patients, 23 had documented CD4 counts, ranging from 2.4% to 45% (median 18.3%) with absolute counts ranging from <1 to 1441 cells/mm³ (median 353). Five patients (5/23, 22%) had absolute CD4 counts under 100 cells/mm³ and one had a count between 101 and 200 cells/mm³, while the remainder had counts more than 200 cells/mm³. Only 14 patients had HIV viral load results available at the start of HL therapy, ranging from

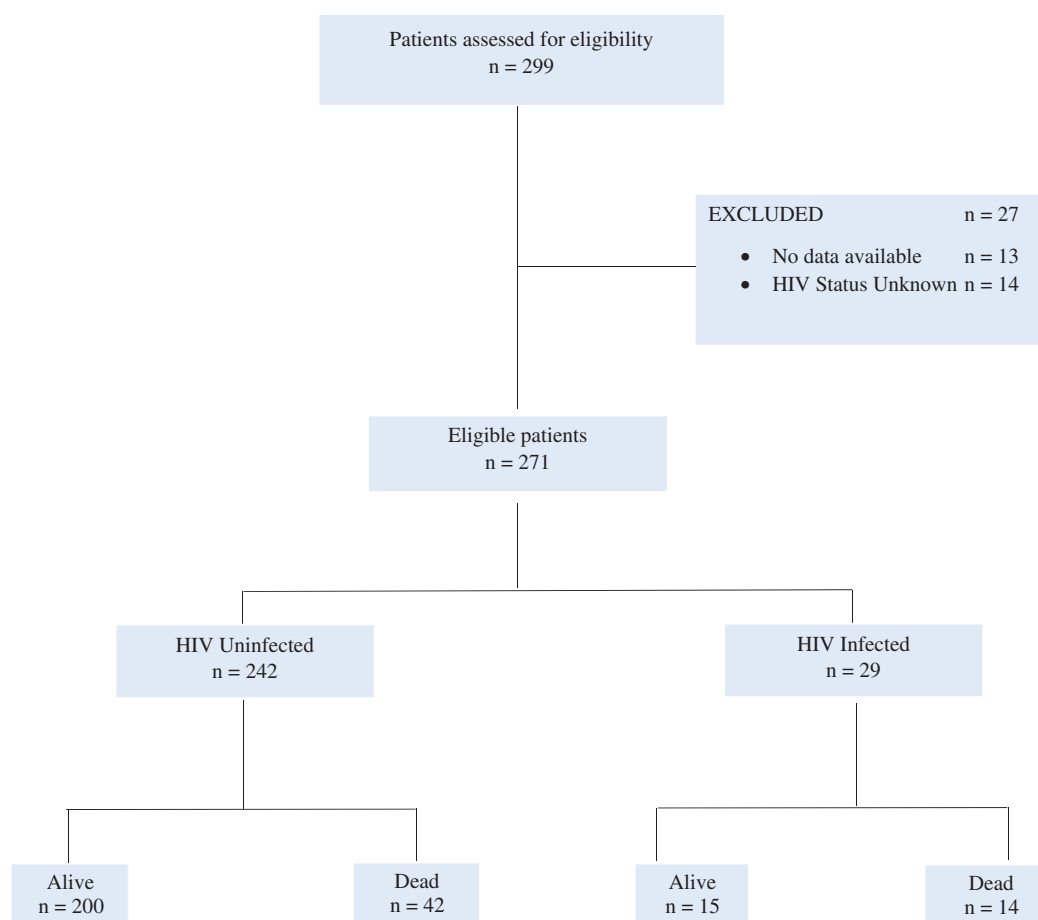


Figure 1. Consort diagram of enrollment, retention, and status at conclusion of follow-up.

undetectable to 656,000 copies/mL. The majority (27/29) presented after 2003 when the national ARV roll-out was firmly established. Eight patients (29%) were receiving ART at the time of diagnosis of HL, and four of these patients were virally suppressed. The length of time each patient was on ART prior to diagnosis was not documented. The remaining 21 patients were commenced on ART concurrently with chemotherapy, except for one patient who abandoned treatment early on.

Management protocols and causes of death

Most patients were treated with ABVD (see Table 1): two patients with HIV (6.6%) and four HIV-uninfected patients (1.7%) died before treatment, and one patient with Stage I nodular lymphocyte-predominant HL had surgical excision and did not require chemotherapy. Tuberculosis was diagnosed and treated in 4/29 (13.8%) HIV-infected patients at the start of treatment; information on tuberculosis was not captured in the HIV-uninfected patients. Both HIV-infected and -uninfected patients received the same chemotherapy protocols, according to institutional preference.

In the HIV-infected cohort, five patients abandoned therapy before completion and the remainder received a median of five cycles of chemotherapy (range 0–8 cycles). Similarly, the HIV-uninfected patients received a median of 5 cycles of chemotherapy.

Overall survival

The 5- and 10-year OS rates for HIV-infected patients were 49% (95% CI 29–65%) and 45% (95% CI 26–62%), respectively, in contrast with 84% (95% CI 78–88%) and 78% (95% CI 72–84%) for the HIV-uninfected group ($p = .0001$) (see Figure 2). The median follow-up was 3.2 years in the HIV-infected group and 6.7 years in the HIV-uninfected group. Causes of death in the 14 HIV-infected children who demised were infection (6), relapsed/progressive disease (1), untreated disease in patients who presented in extremis (2), undocumented (3), and second malignant neoplasm (1) (see Table 2). Based on this small sample, the odds ratio of death by infection in the HIV-infected group was 15 ($p = .004$), and HIV-uninfected patients were more likely to succumb to relapse than

Table 1. Baseline characteristics of children and adolescents with Hodgkin lymphoma.

Parameter	HIV pos n = 29	%	HIV neg n = 242	%	Chi-square p-value
Sex					
Male	22	75.8	184	76.3	.865
Female	7	24.2	57	23.7	.865
Nutritional parameters					
BMI obese/overweight	2	6.9	9	3.7	.413
BMI adequate	23	79.3	180	74.7	.704
BMI <- 2SD	3	10.3	36	14.9	.361
BMI undocumented	1	3.4	16	6.6	.488
Wasting (weight/age <2SD)	9/21 ^a	42.9	26/113 ^a	23.0	.0573
Stunting (height/age <2SD)	15/27 ^a	55.6	79/228 ^a	34.7	.0332
Hypoalbuminemia (<20g/dL)	7/24 ^a	29.2 ^a	22/205 ^a	10.7 ^a	.005
Age					
Median	7.2		10.0		.021
Range	3.3-16.3		2.9-18.8		
Stage					
I	1	3.4	17	7.1	.467
II	5	17.2	92	38.1	.025
III	5	17.2	74	30.7	.136
IV	17	58.6	58	24.1	.000
Unknown	1	3.4	0	0	.004
Histological subtype					
Nodular sclerosing	6	20.7	104	43.2	.019
Mixed cellularity	14	48.3	102	42.3	.530
Lymphocyte depleted	2	6.9	9	3.7	.414
HL NOS	6	17.2	20	8.3	.032
B symptoms					
Yes	20	69.0	144	59.8	.347
No	8	27.6	96	39.8	.208
Undocumented	1	3.4	1	0.4	.072
Bulky disease					
Yes	9	34.5	97	40.2	.347
No	20	65.5	144	59.8	.208
Autoimmune disease					
Yes	6	20.7	26	10.8	.118
No	23	79.3	215	89.2	.118
Treatment					
ABVD	17	56.7	130	53.9	.916
ABVD-ChIVVP	1	3.3	28	11.6	.583
OEPA/OPPA-COPP	9	30.0	79	32.8	.450
Died before treatment initiated	2	6.6	4	1.7	.070

^aDenominators less than the total above reflect missing data.

SD: standard deviations; NOS: not otherwise specified; ABVD: adriamycin, vinblastine, bleomycin, dacarbazine; OPPA/OEPA-COPP: vincristine, procarbazine/etoposide, prednisone, adriamycin-cyclophosphamide, vincristine, prednisone, procarbazine; ABVD-ChIVVP: ABVD-chlorambucil, vinblastine, prednisone, procarbazine.

HIV-infected patients ($p = .044$) but no other significant trend was demonstrated.

Table 3 demonstrates that, although infection was an important cause of death in HIV-infected children, these infections occurred mainly after treatment, indicating that these patients tolerated chemotherapy but succumbed later. Infectious causes of death were culture-negative neutropenic sepsis (2), methicillin-resistant *Staphylococcus Aureus* (1), and *P. jirovecii* with immune reconstitution syndrome (1). One patient demised 3 years post completion of treatment from varicella and *Streptococcus pneumoniae* septicemia.

Poor prognostic features

Although late stage of disease predicted poor survival outcome in the entire cohort [14], the same trend was

not confirmed with statistical significance in the smaller HIV-infected subset of patients (see Table 4). Among HIV-infected patients, an albumin level <20 g/dL ($p = .006$) and a CD4 percentage <15% ($p = .04$) were prognostic of poor survival (see Table 4). Factors that did not achieve statistical significance were: age, sex, race, Ann Arbor stage, B symptoms, bulky disease, histological subtype, treatment site, and nutrition.

Discussion

This report analyzes the largest documented cohort of pediatric HIV-infected patients with HL to date and presents both 5- and 10-year survival data. These patients presented mainly with late-stage disease and the majority was not on ART at the time of diagnosis with HL. The widespread state-sponsored rollout of

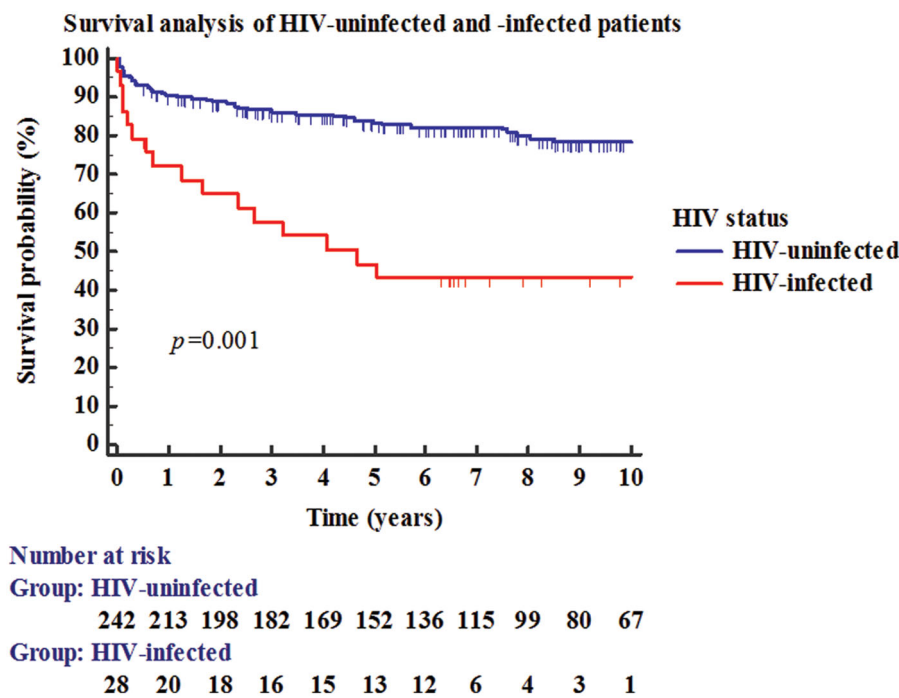


Figure 2. Kaplan–Meier survival analysis of HIV infected and infected pediatric patients.

Table 2. Causes of death in South African children and adolescents with Hodgkin lymphoma.

Causes of death	HIV-infected		HIV-uninfected		Odds ratio	<i>p</i> -value chi square
	<i>n</i> = 14	%	<i>n</i> = 42	%		
Infection	6	42.9	2	4.8	15	0.004
Undocumented	3	21.4	2	4.8	5.45	0.0582
Late presentation	2	14.3	4	9.5	1.58	0.6179
Refractory disease	1	7.1	10	23.8	0.246	0.1740
Second malignancy	1	7.1	0	0	N/A	0.0805
Abandoned therapy	1	7.1	12	28.6	0.0	0.0241
Relapse	0	0	10	23.8	0.0	0.0440
Tuberculosis	0	0	2	4.8	0.0	0.4057

LTFU: lost to follow up.

ART launched in 2003 but did not gain full traction in many parts of the country for some time. AZT is not recommended for use with chemotherapy in high-income settings, however, the ARV regimen containing this agent was the only one available to patients in South Africa at the time. The low 5-year survival rate of 49% may be associated with hypoalbuminemia and low CD4 percentages at diagnosis. The most prominent causes of death were infection in the HIV-infected patients and relapsed/refractory disease in HIV-uninfected patients; although these numbers are small and conclusions should be interpreted with reserve. It is important to note that most of the deaths in the HIV-infected children occurred in the period 18–50 months post completion of therapy, which implies that they were not related to the cancer or treatment thereof.

Adults with HL and HIV were reported to have similar 5-year OS rates to their HIV-uninfected counterparts [16]. In contrast, in this study, pediatric patients

with HIV and HL had a significantly lower survival rate than both HIV-uninfected children with HL and HIV-infected children without HL. It was also markedly lower than that of patients with HL and HIV reported in a South African study [10] although only 12 patients from seven South African centers were reported. ART was made widely available in South Africa in 2003 [17] and good coverage was initially achieved, though this has not been sustained [18]. Although the early initiation of ART has been shown to improve outcomes of HIV-infected children with cancer [10,19], only 8/29 patients in this study were on ART at presentation; however, all patients who received chemotherapy were also initiated on ART.

Bohlius et al. [12] reported that children who were on ART were less likely to develop cancer than children who were not on ART. HL is not considered an AIDS-defining malignancy in either adults or children, despite an excess of HL being demonstrated in these

Table 3. Details of demised South African HIV-infected children and adolescents with Hodgkin lymphoma, diagnosed 2000–2010.

Age (years)	Nutritional status				On ART at diagnosis	CD4 (%)	HIV viral load	TB	Chemotherapy	Cause of death	Survival time (months)
	Wasting wt/age	Stunting ht/age	BMI/age	Stage							
8.5	severe	severe	severe	IV	N	29	2,45,465	N	OEPA-COPP	Progression of disease	8.2
8.4	severe	moderate	adequate	IV	Y	20.8	UDL	N	ABVD	Progression of disease	14.8
3.3	overweight	adequate	adequate	IV	Y	3.9	1,54,542	N	OEPA-COPP	Acinetobacter septicemia	48.9
6.5	moderate	adequate	adequate	IV	N	N/D	N/D	N	OEPA-COPP	Neutropenic sepsis, culture negative	28.0
6.5	adequate	moderate	adequate	IV	N	N/D	2,57,078	N	OEPA-COPP	Second malignancy: primitive neuroectodermal tumor of the central nervous system	55
3.8	adequate	moderate	adequate	II	N	14	N/D	N	ABVD	<i>S. pneumoniae</i> and varicella septicemia	38.7
4.5	moderate	adequate	adequate	IV	N	45	N/D	N	ABVD	Abandoned therapy	1.1
13.3	N/A	adequate	adequate	II	N	10.7	N/D	N	ABVD	Not documented	60.5
13.4	N/A	adequate	obese	IV	N	16	1,97,000	N	ABVD	Abandoned therapy	2.3
7.8	adequate	severe	adequate	IV	Y	11	140	Y	ABVD	Neutropenic sepsis, methicillin resistant <i>Staphylococcus aureus</i>	0.7
6.2	moderate	severe	adequate	II	Y	N/D	N/D	N	ABVD	Not documented	19.7
5.8	adequate	adequate	adequate	III	N	N/D	N/D	Y	ABVD	<i>Pneumocystis jirovecii</i> immune reconstitution syndrome	17.9
7.2	adequate	adequate	adequate	N/D	N	12	N/D	Y	ABVD	Not documented	3.4
11.0	N/A	N/D	N/D	IV	N	N/D	N/D	N	Died before chemotherapy	Progression of disease (presented in extremis)	0.9
3.8	moderate	moderate	adequate	IV	Y	18.3	UDL	Y	Died before chemotherapy	Progression of disease (presented in extremis)	0.03

BMI: body mass index; UDL: under detectable limit; N/D: not documented/done; TB: tuberculosis; ABVD: adriamycin, vinblastine, bleomycin, dacarbazine; OEPA/OEPA-COPP: vincristine, procarbazine/etoposide, prednisone, adriamycin-cyclophosphamide, vincristine, prednisone, procarbazine.

populations [20]. The prevalence of HIV infection (10.7%) in the entire HL cohort was higher than that in the South African pediatric population during the study [21] but the expected referral bias precludes accurate prevalence estimates. In an HIV-endemic region such as South Africa, conditions such as HIV lymphadenopathy, reactive lymphoid hyperplasia, and tuberculosis may mask the presentation of HL [22], which may have contributed to the increased proportion of patients with late presentation.

Although hypoalbuminemia is a recognized risk factor for poor prognosis in childhood HL [19], this must be used in conjunction with various other parameters in a locally specific manner, as albumin levels may be low in malnutrition, decreased as part of an acute-phase reaction, and may also reflect cachexia from advanced disease. We postulate that children with HIV are more likely to present with hypoalbuminemia (see Table 1), due to both malnutrition associated with HIV infection and late presentation, and that this may contribute to increased chemotherapy toxicity through various mechanisms.

Limitations of this study are the small numbers of HIV-infected patients reported and a possible sampling bias as all patient data was sourced from referral hospitals. It is also likely that many patients with HL were not diagnosed or referred to specialist centers as the rate of under-ascertainment of cases was high during this period [23]. Some records were incomplete, resulting in missing data, most notably CD4 counts and HIV viral loads, which would have been helpful in analyzing prognosis. The lack of prognostic impact of clinical signs of malnutrition (wasting, stunting, and low BMI) (Table 4) was unexpected but the most accurate measure of malnutrition in children with cancer, mid-upper arm circumference [24], was not recorded in these patients. It is possible that the use of three different chemotherapy protocols may have impacted on survival, especially as this was a finding in the larger study [14], but the sub-study was not powered to detect this difference. The numbers were also too small to determine whether being on ART at time of diagnosis of HL impacted positively on prognosis.

As HIV is a condition affecting large numbers of children in low and middle-income countries, and childhood cancer is receiving increasing attention, it is essential to initiate the process of creating guidelines for the management of these patients. The approach to treating children with HL and comorbid infection with HIV is underpinned with the awareness that HL in patients with AIDS is an aggressive disease with high mortality due to infection. The interplay of

Table 4. Univariate risk factor analysis of HIV positive pediatric patients with HL.

Variable	5 year OS (%)	Hazard ratio	95% CI, upper	95% CI, lower	p-value Cox regression
Sex					
Male	50.6	Ref			.9655
Female	42.9	1.026	0.3260	3.278	
Age					
<10 years	45.0	1.1063	0.3663	3.3407	.9806
>10 years	60.0	Ref			
Body mass index					
Moderate, severe decrease	66.7	0.5420	0.071	40145	.5053
Adequate, overweight	46.1	Ref			
Weight/age					
Moderate, severe decrease	44.4	1.2460	0.3780	4.111	.536
Adequate, overweight	50.0	Ref			
Height/age					
Moderate, severe decrease	50.3	Ref			
Adequate	50.0	1.007	0.3490	2.906	.9896
Ann Arbor stage					
Stage I and II	66.7	Ref			.5312
Stage III and IV	45.5	1.4396	0.4601	4.5041	
B symptoms					
Yes	42.1	1.7800	0.4950	6.395	.3051
No	72.9	Ref			
Bulky disease					
Yes	44.4	1.162	0.412	3.3276	.7758
No	50.8	Ref			
Autoimmune disorders					
Yes	16.7	2.226	0.754	6.569	.1472
No	55.3	Ref			
CD4 percentage					
<15%	37.5	1.7867	0.5862	5.4457	.0412
>15%	65.5	Ref			
On ART at diagnosis of HL					
No	37.5	0.7185	0.2315	2.2297	.5672
Yes	50.6	Ref			
Albumin level					
<20 g/dL	0.0	4.621	1.409	15.154	.0060
>20 g/dL	65.5	Ref			
Chemotherapy regimen					
ABVD	54.5	1.032	0.356	2.988	.9537
OPPA/OEPA-COPP	25.0	1.582	0.543	4.610	
ABVD-ChIVPP	100	Ref			

Ref: reference value; ART: antiretroviral therapy; ABVD: adriamycin, vinblastine, bleomycin, dacarbazine; OPPA/OEPA-COPP: vincristine, procarbazine/etoposide, prednisone, adriamycin-cyclophosphamide, vincristine, prednisone, procarbazine

environment, infections, nutrition, and the immune dysregulation of HL [25] with the immune compromise of HIV must also be taken into account. The progressive loss of both humoral and cellular immunity experienced by children with HIV on chemotherapy progressively increases the risk of infection, making these children more vulnerable to infection-associated treatment-related mortality. HIV-uninfected children, in contrast, recover their immunity between cycles of chemotherapy [3].

Although current guidelines recommend that all children with HIV initiate ART, regardless of the CD4 count, only 54% of children with HIV worldwide currently receive ART [26] and 31% (8/29) of our patients were on ART at time of diagnosis. Initiating children with HIV on ART also allows them to be more successfully treated with chemotherapy [10,19] although we were unable to test this hypothesis in this study due to small sample size.

If viral suppression has not been achieved in those patients already on ART, and adherence has been assured, it may be prudent to consider resistance testing if available and/or changing to a second-line ART regimen. ART should be initiated at diagnosis in those patients who have not yet commenced on ART. Instead of giving aggressive chemotherapy such as bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone (BEACOPP) [27] or doxorubicin, bleomycin, vincristine, etoposide, cyclophosphamide, prednisone (ABVE-PC) [28] to high-risk patients, especially in settings where G-CSF and supportive care is not consistently available, the clinician could consider giving less toxic chemotherapy such as ABVD and consolidating with radiotherapy [29], if available. The use of G-CSF is considered standard of care in many well-resourced settings, but it was not widely available in South Africa at the time of the study. It is essential to pay very close attention to the

prevention and treatment of opportunistic infections such as tuberculosis and *P. jirovecii*, as well as being aware of the devastating consequences of viral infections such as varicella, both during and after treatment of HL. A multidisciplinary team comprising oncologists, HIV clinicians, and infectious diseases specialists is desirable to ensure that both the expected infections associated with neutropenia and HIV-specific opportunistic infections are adequately managed.

In summary, the lower survival rate of South African pediatric patients with HIV who develop HL appears to be associated with a CD4 percentage <15% and hypoalbuminemia. Children with HIV in this cohort demonstrated increased mortality from infection, while those without HIV were more likely to demise from relapsed/progressive disease. For more definitive results, it would be necessary to enroll more patients prospectively in a multicenter, multinational study to accurately determine reasons for poor outcomes, and modern risk group assessment should be used to ensure results are comparable across studies. Standard treatment for HL in HIV-infected children has not yet been defined and it is hoped that the findings from this study will aid in the development of strategies to improve survival among those diagnosed with HL and HIV in similar settings.

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Disclosure statement

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ORCID

Jennifer Ann Geel  <http://orcid.org/0000-0001-8792-3251>
 Katherine Claire Eyal  <http://orcid.org/0000-0003-1974-5195>
 Marc Gerald Hendricks  <http://orcid.org/0000-0002-3636-0994>
 Khumo Hope Myezo  <http://orcid.org/0000-0002-2180-5743>

David Kenneth Stones  <http://orcid.org/0000-0001-7423-2291>
 Fareed Omar  <http://orcid.org/0000-0002-2319-1087>
 Yasmin Goga  <http://orcid.org/0000-0002-6740-2376>
 Anel van Zyl  <http://orcid.org/0000-0003-3370-0874>
 Barry van Emmenes  <http://orcid.org/0000-0002-0217-347X>
 Shaegan Irusen  <http://orcid.org/0000-0001-6205-3181>
 Rossella Marina Bandini  <http://orcid.org/0000-0001-6240-9408>
 Oloko Wedi  <http://orcid.org/0000-0003-3644-5565>
 Bianca Rowe  <http://orcid.org/0000-0001-8161-0596>
 Daynia Elizabeth Ballot  <http://orcid.org/0000-0003-4985-048X>
 Monika L. Metzger  <http://orcid.org/0000-0002-7102-4611>

References

- [1] Carbone A, Gloghini A, Caruso A, et al. The impact of EBV and HIV infection on the microenvironmental niche underlying Hodgkin lymphoma pathogenesis. *Int J Cancer*. 2017;140(6):1233–1245.
- [2] Gougeon M-L, Montagnier L. Programmed cell death as a mechanism of CD4 and CD8 T cell deletion in AIDS: molecular control and effect of highly active anti-retroviral therapy. *Ann NY Acad Sci*. 1999;887(1): 199–212.
- [3] Chanock S, Pizzo P. Infection prevention strategies for children with cancer and AIDS: contrasting dilemmas. *J Hosp Infect*. 1995;30:197–208.
- [4] UNAIDS data 2019 [Internet]. Rstesa.unaids.org. 2020 [cited 2020 Dec 1]. Available from: <http://rstesa.unaids.org/publications/global-publications/2019/item/208-unaids-data-2019>
- [5] Villamor E, Misegades L, Fataki MR, et al. Child mortality in relation to HIV infection, nutritional status, and socio-economic background. *Int J Epidemiol*. 2004; 34(1):61–68.
- [6] Hosegood V. The demographic impact of HIV and AIDS across the family and household life-cycle: implications for efforts to strengthen families in sub-Saharan Africa. *AIDS Care*. 2009;21:13–21.
- [7] Richter L. The impact of HIV/AIDS on the household. *Aids Bull*. 1997;6(4):20–23.
- [8] Chiappini E, Galli L, Tovo P, et al. Cancer rates after year 2000 significantly decrease in children with perinatal HIV infection: a study by the Italian register for HIV infection in children. *J Clin Oncol*. 2007;26(1): 97–101.
- [9] Mayosi BM, Lawn JE, Van Niekerk A, et al. Health in South Africa: changes and challenges since 2009. *Lancet*. 2012;380(9858):2029–2043.
- [10] Davidson A, Wainwright RD, Stones DK, et al. Malignancies in South African children with HIV. *J Pediatr Hematol Oncol*. 2014;36(2):111–117.
- [11] Mbulaiteye SM, Katabira ET, Wabinga H, et al. Spectrum of cancers among HIV-infected persons in Africa: the Uganda AIDS-Cancer Registry Match Study. *Int J Cancer*. 2006;118(4):985–990.
- [12] Bohlius J, Maxwell N, Spoerri A, et al. Incidence of AIDS-defining and other cancers in HIV-positive

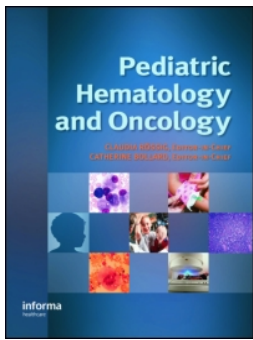
- children in South Africa. *Pediatr Infect Dis J*. 2016; 35(6):e164–170.
- [13] Arico M, Caselli D, Argenio PD, et al. Malignancies in children with human immunodeficiency virus type 1 infection. *Cancer*. 1991;68(11):2473–2477.
- [14] Geel JA, Chirwa TC, Rowe B, et al. Treatment outcomes of children with Hodgkin lymphoma between 2000 and 2010: first report by the South African Children's Cancer Study Group. *Pediatr Blood Cancer*. 2017;64(10):e26536.
- [15] Flerlage JE, Howard SC, Punnett A, et al. Staging evaluation and response criteria harmonization (SEARCH) for childhood, adolescent and young adult Hodgkin lymphoma (CAYAHL): methodology statement. *Pediatr Blood Cancer*. 2017;64(7):e26421–10.
- [16] Olszewski AJ, Castillo JJ. Outcomes of HIV-associated Hodgkin lymphoma in the era of antiretroviral therapy. *AIDS*. 2016;30(5):787–796.
- [17] Bekker LG, Venter F, Cohen K, et al. Provision of antiretroviral therapy in South Africa: the nuts and bolts. *Antivir Ther*. 2014;19(3):105–116.
- [18] Johnson LF, Dorrington RE, Moolla H. Progress towards the 2020 targets for HIV diagnosis and antiretroviral treatment in South Africa. *South Afr J HIV Med*. 2017;18(1):1–8.
- [19] Schwartz CL, Chen L, McCarten K, et al. Childhood Hodgkin International Prognostic Score (CHIPPS) predicts event-free survival in Hodgkin lymphoma: a report from the children's oncology group. *Pediatr Blood Cancer*. 2017;64(4):e26278.
- [20] Simard EP, Shiels MS, Bhatia K, et al. Long-term cancer risk among people diagnosed with AIDS during childhood. *Cancer Epidemiol Biomarkers Prev*. 2012; 21(1):148–154.
- [21] Shisana O, Rehle T, Simbayi L, et al. South African national HIV prevalence, incidence and behaviour survey. Cape Town, South Africa: HSRC Press; 2014. p.194.
- [22] Buyego P, Nakiyingi L, Ddungu H, et al. Possible misdiagnosis of HIV associated lymphoma as tuberculosis among patients attending Uganda Cancer Institute. *AIDS Res Ther BioMed Central*. 2017;14(13):10–15.
- [23] Stefan D, Stones D, Wainwright R, et al. Childhood cancer incidence in South Africa, 1987–2007. *South Afr Med J*. 2015;105(11):939.
- [24] Oguz A, Karadeniz C, Pelit M, et al. Arm anthropometry in evaluation of malnutrition in children with cancer. *Pediatr Hematol Oncol*. 1999;16(1):35–41.
- [25] Vardhana S, Younes A. The immune microenvironment in Hodgkin lymphoma: T cells, B cells, and immune checkpoints. *Haematologica*. 2016;101(7): 794–802.
- [26] Paediatric care and treatment: just over half (54 per cent) of children under 15 years of age living with HIV are on antiretroviral medications. [Internet]. UNICEF. 2019. Available from: <https://data.unicef.org/topic/hiv/aids/paediatric-treatment-and-care/>
- [27] Kelly KM, Spoto R, Hutchinson R, et al. BEACOPP chemotherapy is a highly effective regimen in children and adolescents with high-risk Hodgkin lymphoma: a report from the children's oncology group. *Blood*. 2011;117(9):2596–2603.
- [28] Schwartz CL, Constine LS, Villaluna D, et al. A risk-adapted, response-based approach using ABVE-PC for children and adolescents with intermediate- and high-risk Hodgkin lymphoma: the results of P9425. *Blood*. 2009;114(10):2051–2059.
- [29] Hentrich M, Berger M, Wyen C, et al. Stage-adapted treatment of HIV-associated Hodgkin lymphoma: results of a prospective multicenter study. *J Clin Oncol*. 2012;30(33):4117–4123.

Chapter 4. Feasibility

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Jennifer Geel^a , Marc Hendricks^b , Yasmin Goga^c , Beverley Neethling^d , Vutshilo Netshituni^e , Rema Mathew^f, Johani Vermeulen^g , Anel van Zyl^h , Fareed Omarⁱ , Jan du Plessis^j , Liezl du Plessis^k, Elelwani Madzhia^l, Thandeka Ngcana^m , Thanushree Naidooⁿ, Lizette Louw^o, Daynia E. Ballot^p , and Monika L. Metzger^q 

^aPediatric Haematology-Oncology, University of the Witwatersrand, Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg, South Africa; ^bPediatric Haematology-Oncology, University of Cape Town, Red Cross War Memorial Children's Hospital, Cape Town, South Africa; ^cPediatric Haematology-Oncology, University of KwaZulu-Natal, Inkosi Albert Luthuli Hospital, Durban, South Africa; ^dPediatric Haematology-Oncology, University of KwaZulu-Natal, Durban, Inkosi Albert Luthuli Hospital and Greys Hospital, Pietermaritzburg, South Africa; ^ePediatric Haematology-Oncology, University of Limpopo, Polokwane-Mankweng Hospital Complex, Polokwane, South Africa; ^fPediatric Haematology-Oncology, Walter Sisulu University, Frere Hospital, East London, South Africa; ^gPediatric Haematology-Oncology, Walter Sisulu University, Dora Nginza Hospital, Qheberha, South Africa; ^hPediatric Haematology-Oncology, University of Stellenbosch, Tygerberg Hospital, Cape Town, South Africa; ⁱPediatric Haematology-Oncology, University of Pretoria, Steve Biko Academic Hospital, Pretoria, South Africa; ^jPediatric Haematology-Oncology, University of the Free State, Universitas Hospital, Bloemfontein, South Africa; ^kPediatric Haematology-Oncology, University of the Free State, Kimberley Hospital, Kimberley, South Africa; ^lPediatric Haematology-Oncology, Sefako Makgatho University, Dr George Mukhari Hospital, Garankuwa, South Africa; ^mPediatric Haematology-Oncology, University of the Witwatersrand, Chris Hani Baragwanath Academic Hospital, Johannesburg, South Africa; ⁿDepartment of Radiation Oncology, University of the Witwatersrand, Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg, South Africa; ^oDepartment of Nuclear Medicine, University of the Witwatersrand, Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg, South Africa; ^pSchool of Clinical Medicine, University of the Witwatersrand, Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg, South Africa; ^qMedecins sans Frontieres, Democratic Republic of the Congo

ABSTRACT

Introduction: Collaborative studies have contributed to improved survival of pediatric Hodgkin lymphoma in well-resourced settings, but few are documented in resource-constrained countries. The South Africa Children's Cancer Study Group initiated harmonization of management protocols in 2015. This article analyzes barriers and enablers of the process. **Methods:** Clinician-researchers at 11 state-funded pediatric oncology units completed preparatory questionnaires in June 2018. Parameters included infrastructure, access to therapeutic modalities and clinician numbers. A reassessment of 13 sites (two new pediatric oncology unit) in February 2021 ascertained changes in resources and identified challenges to full participation. Questions investigated the presence and quality of diagnostic radiology, availability of surgeons, cytology/pathology options and hematology laboratory facilities. **Results:** The response rate was 11/11 to survey 1 and

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South Africa

CONTACT Jennifer Geel  jennifer.geel@wits.ac.za  Pediatric Haematology-Oncology, University of the Witwatersrand, Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg, South Africa

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13/13 to survey 2. The anticipated pre-study barriers to participation of pediatric oncology units included time constraints and understaffing. PET-CT was unavailable to two centers. The majority of pediatric oncology units met the minimum criteria to participate. The interim survey confirmed chemotherapy and radiotherapy availability nearly 100% of the time. One site reported improved access to radiotherapy while another reported improved access to PET-CT. Barriers to participation included excessive times to obtain regulatory approvals, time constraints and lack of dedicated research staff. Enablers include the simple management algorithm and communication tools.

Conclusion: This study demonstrates that multicenter collaboration and harmonization of management protocols are achievable in a middle-income setting. Minimal funding is required but full participation to run high-quality studies requires more financial investment. Focused funding and increased prioritization of research may address systemic barriers to full participation.

Introduction

Childhood cancer 5-year overall survival in high-income countries (HIC) has improved steadily from approximately 30% in the 1960s to 90% in the 21st century.¹ Much of this improvement is attributable to collaborative work, as childhood cancer is rare and recruitment of sufficient patients to achieve statistical significance requires multicenter collaboration. Since the 1970s, HL has been treated in cooperative group trials, leading to successively higher survival rates.² Groups such as the EuroNet Pediatric Hodgkin Network and the North America Children's Oncology Group have conducted multiple consecutive trials documenting improved survival rates exceeding 95%.³

The growing movement toward adapted treatment regimens in low-and-middle-income countries (LMIC) includes ATRs for HL, successfully used in Latin America.⁴ While many ATRs are positioned as very simplistic guidelines suitable for highly resource-constrained settings, few have been explicitly positioned in the middle-income (MIC) or upper-middle-income (UMIC) setting, such as South Africa. The majority of children with cancer in HIC are enrolled on prospective clinical trials as matter of course,⁵ while this is not the case in Africa or Asia.

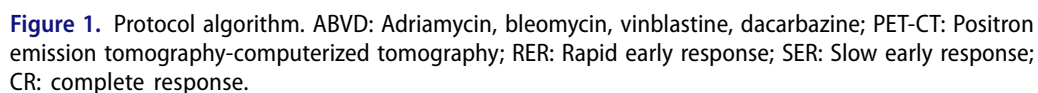
"Harmonization" refers to a growing effort to employ the same standards and norms in diagnosing and treating various cancers. The term may also include the minimizing of redundant or conflicting standards that may have evolved independently. By introducing a harmonized national protocol, the intention is to achieve comparable survival outcomes to those realized in other countries (both HIC and MIC) and to standardize laboratory and imaging diagnostic tests.

Survival rates for children and adolescents with HL in South Africa range from 20% in under-resourced settings to 80% in established centers.⁶ Harmonization of management protocols in a research setting has been identified as an approach to improve survival rates, decrease toxicity and streamline costs. There are no published African studies indicating that the use of a single risk-adapted, response-based protocol is feasible or whether national survival rates can be improved to approach those in HIC with such a strategy. This article outlines the implementation of a multicenter, national protocol and aims to

The South African HL prospective study protocol comprises a simple, risk-stratified, response-adapted approach to improve survival rates, paying particular attention to patients with HIV infection and advanced disease at presentation. This particular sub-study compared resources necessary to conduct a multicenter observational study at initiation and partway through the project process to assess whether harmonization is feasible in South Africa.

Design of the prospective observational study SACCSG-HL2018

SACCSG-HL2018 was designed as a multicenter observational study to harmonize treatment approaches in South Africa, with an inbuilt feasibility assessment. The model proposed by Chung⁷ was followed to plan the study. Three protocol meetings were held on 08/03/2016, 08/08/2016 and 15/09/2016 to interrogate results of the retrospective data and to plan the prospective protocol. Risk grouping was based on Pediatric Hodgkin Consortium risk assessment, with Standard Risk comprising Cotswold-modified Ann Arbor stage IA, IB and IIA; Medium Risk comprising Stage IX, IE, IIX, IIE and IIIA, and High Risk comprising Stage IIEEX, Stage IIIB, IIIX, IIIE and Stage IV.² The simple treatment algorithm was designed to avoid errors (see [Figure 1](#)) favoring administration of chemotherapy in an out-patient setting.



All children and adolescents with biopsy-proven, treatment-naïve HL are included, including those with HIV infection. Exclusion criteria included those with preexisting cardiac dysfunction precluding treatment with anthracyclines and those with nodular lymphocyte predominant HL.

Patients with bulky disease, mediastinal masses and/or incomplete response based on interim PET-CT receive consolidation therapy with 25 Gy radiotherapy, preferably involved node or involved field, according to the capability of each unit.

The study was linked to a PhD project to enhance academic rigor, increase research capacity and attract grant funding. During the protocol development a supervisor (MM) with experience in LMIC collaborative studies, an economics expert (KE) and a statistician (TK) with experience in LMIC studies were included to contribute expertise in a study for resource-limited settings.

Prognostic markers with proven prognostic value in resource-constrained settings that were included were total white cell count, total lymphocyte count, hemoglobin, platelet count, absolute eosinophil count, erythrocyte sedimentation rate, copper, ferritin and lactate dehydrogenase. The ongoing observational prospective study aims to determine whether a harmonized protocol leads to better survival outcomes and whether alterations in these affordable, readily available blood tests correlate with PET-CT findings. If so, it is postulated that PET-CT could safely be omitted in settings that cannot perform this modality in patients classified as rapid early responders in a similar way that thymus and activation-regulated chemokine/CCL17 (TARC) levels have been used.⁸

A REDCap® database⁹ was created to collect data which included treatment response and toxicities, survival outcome and adherence to the protocol. A pilot study was initiated in three pediatric oncology units on the University of the Witwatersrand circuit, and the REDCap® study database was iteratively adapted to ensure ease of use and accuracy of data. Specific features, new in this context, included body surface area calculators, International Classification of Disease codes and chemotherapy dose calculators. Central review of radiology and pathology was facilitated by uploading images and reports.

Participants in the feasibility sub-study

An invitation was sent to all state-funded pediatric oncology units to participate, each represented by a clinician-researcher and, without exception, all committed to the project. Study participants (clinician-researchers) including the principal investigator (PI), completed a brief survey to determine if their pediatric oncology unit met the criteria for participation (see [Table 1](#), [Supplementary material](#)) in the prospective study.

Once the majority of pediatric oncology units had started enrolling patients, online meetings were held to incorporate ongoing quality assurance as problems or learning areas were detected. A WhatsApp® group was created to encourage rapid communication and updates, and participants were offered co-authorship on articles if they met the accepted publication criteria.¹⁰ All participants signed an agreement to participate, communicate and collaborate.

Design of feasibility sub-study

The questions for the first survey were based on the pre-requisites in [Table 1](#) ([Supplementary material](#)), to determine whether participating pediatric oncology unit

had sufficient staff, treatment modalities and infrastructure to follow the treatment protocol. Open-ended questions regarding challenges and solutions were posed. Survey 1 was created in REDCap to facilitate rapid responses and collation of data, and was conducted from 1 to 15 June 2018.

Once all sites opened for recruitment, a second telephonic assessment was conducted between 1 and 28 February 2021 by the PI. The telephonic format was favored to elicit more nuanced responses, to enhance communication and try to devise solutions to problems in real time. This survey ascertained changes in infrastructure and resources identified challenges to full participation in the study. New questions were added to this questionnaire in response to protocol violations detected in the interim analysis. These violations included blood tests not being taken as specified in the protocol, PET-CT not being performed according to protocol and radiotherapy not being administered when indicated.¹¹ In addition, the capacity to consent and enroll study participants was assessed. These questions investigated the presence and quality of diagnostic radiology (X-ray, PET-CT), availability of surgeons, cytology/pathology options, hematology and chemistry laboratory facilities. Further data points included time to ethics committee approvals, physical infrastructure, treatment modalities and staffing levels. Open-ended questions were posed to elicit other challenges not covered in the preceding questions, as well as potential solutions.

Ethics and regulatory approvals

The study was approved by a scientific committee (postgraduate committee of the University of the Witwatersrand, “Wits”) and the Wits human research ethics committee (M1711100) and registered on the National Health Research Database and the seven provincial Health Research Databases of each pediatric oncology unit. Approval was obtained by the national PI from the ethics committee of each participating pediatric oncology unit.

Results

Pre-study questionnaire 1

The response rate to the first questionnaire was 100% (11/11 pediatric oncology units), and all fields were completed (see [Table 1](#)). Multiple respondents indicated severe understaffing, with a median of two full-time consultants and one medical officer per pediatric oncology unit, responsible for 26–150 new oncology patients annually and training a median of one fellow. Appropriate diagnostic radiological services (basic radiographs and PET-CT) were available in all 11 pediatric oncology units while staging PET-CT was readily available to 9/11 pediatric oncology units, with plans to transport patients to the nearest nuclear medicine facility in the remaining two pediatric oncology units. All participants reported access to the necessary chemotherapy agents, while radiotherapy was available 100% of the time in 9/11 pediatric oncology units and 75% of the time in 2/10 pediatric oncology units (see [Tables 1](#) and [2](#)). It was thus concluded that the majority of pediatric oncology units met the minimum requirements to participate.

Table 1. Preplanning survey 2018 prior to national rollout of study (2018).

Staffing	Median	Range
Number of full time consultants in unit	2	2–4
Number of registered pediatric oncologists/hematologists in unit	2	1–4
Number of senior registrars/fellows in the unit	1	1–2
Number of permanent medical officers in the unit	1	1–2
	Number	Percentage
Number of new oncology patients per year		
26–50	2	16.7
51–75	3	25.0
76–100	1	8.3
101–125	2	16.7
126–150	3	25.0
>150	1	8.3
Diagnostic modalities		
Access to appropriate radiological services, including review/ reports		
Chest X ray	11	100
CT scans	11	100
MRI	11	100
Access to PET CT		
Yes	9	82
No	2	18
Access to ABVD medications		
100% of the time	11	100
Access to COPDac medications		
100% of the time	11	100
Access to radiotherapy a reasonable distance from the pediatric oncology unit		
Up to 100% of the time	9	82
Up to 75% of the time	2	18
Type of radiotherapy available		
Involved node	2	18
Involved field	6	55
Involved region	3	27
Regular multidisciplinary team meetings held		
Yes	8	73
No	3	27
Access to pediatric intensive care facilities		
100% of the time	6	55
75% of the time	1	9
50% of the time	4	36

Mid-study questionnaire 2

The second questionnaire to participants from 13 sites, which included the original 11 sites and two new pediatric oncology units that had been established since the start of the project. The response rate was 13/13 (100%) and all questions were answered (see Table 3). Participants reported that all patients approached to enroll on the study agreed to participate.

The essential diagnostic modalities were available in the majority of sites. The required chemotherapy agents were available nearly 100% of the time, with all pediatric oncology units reporting a temporary shortage of doxorubicin from January to March 2020 due to a nationwide shortage. This shortage affected three patients for one cycle each and the patients remained on study. Access to radiotherapy was unchanged, with one site reporting improved access. One pediatric oncology unit that previously reported no access to PET-CT scans elected to transport patients to a referral center for this modality, while another still had no access, despite repeated requests and motivations to hospital management, thus

Table 2. Preplanning survey free text questions prior to national rollout of study (2018).

"Which barriers or challenges do you foresee?"	n = 11	%
Time constraints due to understaffing, high clinical and teaching load	4	36
Time constraints, unspecified	4	36
No barriers	3	27
Patient transport costs	3	27
No PET-CT facilities available	2	18
HREC approvals a long and complicated process	2	18
Adherence of patients to treatment a concern	1	9
No study nurses	1	9
Radiotherapy services are constrained	1	9
Serum copper not done at local laboratory	1	9
"Which potential solutions to the problems you have mentioned can you put forward?"		
Solutions that may be achievable through the study		
Research assistance.		
Provide a broad plan of where we are going to and how each part fits in.		
Streamline and simplify processes as much as possible.		
Discuss with chemical pathology laboratories how to get serum copper tests done.		
Systemic solutions that require government/other funding		
PET-CT scanning facilities within reasonable distance of the pediatric oncology unit.		
Improved staffing complement (pediatric oncologists, pediatric radiation oncologists, pediatric oncology trained nurses).		
Data capturer		
Administrative support		
"If we were to access more funding for this project, are there are any specific things you would like funded to assist you to take part in this project?"		
Full time research coordinator		
Data capturer		
Administrative support		
Funding for traveling to group meetings, should it be required		
Assistance with counseling and ethics/ consent discussions		
Transport funding for patients to get to PET CT scans		
More nurses		
"Do you have any particular comments or suggestions to make this project a success?"		
Everyone needs to contribute		
Prompt registration of patients, to be up to date and efficient with data collection, constant contact with and feedback from PI.		
Regular meetings		

making 12/13 sites eligible for participation. Multiple responses indicated that, although the management algorithm had been formally introduced in all radiation departments, many individual radiation oncologists still did not agree to radiate certain patients as they did not agree with the indications for consolidation radiotherapy in these patients.

Enablers

Enablers of the project were the simple management algorithm, data-capture tool and communication methods. These methods included addressing protocol violations with individual researchers, WhatsApp® communications and team meetings for issues that pertained to many pediatric oncology units. Barriers to full participation included protracted time periods to receive regulatory approvals, severe time constraints, lack of research support staff and lack of PET-CT facility within a reasonable distance of one center. The added strain of the COVID-19 pandemic was reported by many participants as a potential factor for incomplete data capture, but it did not affect recruitment.

Table 3. Survey 2 2021 after national rollout of study.

Diagnostic modalities	n	%
Chest x-ray facilities available	13	100
Fine needle aspiration (FNA) biopsy results		
Good quality results within 72 hours	2	15
Good quality results within 7 days	1	8
Results often inconclusive	7	54
No longer perform FNA as results are inconclusive	3	23
Surgeons available to perform lymph node excisions		
Pediatric surgeons available in the hospital	10	77
General surgeons available in the hospital	2	15
Refer to another hospital for excision	1	8
Histopathology services		
Good quality results within 7 days	9	69
Good quality results within 14 days	3	23
Adequate quality results within 14 days	1	8
PET-CT facilities available		
Fused PET-CT in treating center	8	61
Refer to another center for PET-CT	4	31
PET-CT not available	1	8
Full blood count and differential available	13	100
Regulatory requirements		
Time to university ethics permission <6 months	11	85
Time to university ethics permission >18 months	2	15
Provincial ethics committees permission obtained <6 months (n=8)	8	62
Good Clinical Practice or ethics course completed in the last 5 years	10	77
Good Clinical Practice or ethics course not completed in last 5 years	4	31
Enrollment		
1–27 patients (median 3.5)	11	85
0 patients	2	15
Infrastructure and staff		
Sufficient out-patient facilities to participate in the study	12	92
Insufficient out-patient facilities to participate in the study	1	8
Sufficient in-patient facilities to participate in the study	13	100
Sufficient nurses and doctors to participate in the study	11	85
Insufficient nurses and doctors to participate in the study	2	15
Pediatric oncology unit holds regular multidisciplinary team meetings	11	85
Pediatric oncology unit does not hold regular multidisciplinary team meetings	2	15
Oncology trained nurses per shift		
More than one	9	69
At least one	2	15
None	2	15
Research infrastructure		
Sufficient internet access to upload data on REDCap	12	92
Insufficient internet access to upload data on REDCap	1	8
Trained in the use of REDCap	13	100
Confident in the use of REDCap	8	62
Request REDCap refresher	4	31
Limited availability of research support staff	4	31
No availability of research support staff	10	77
Chemotherapy and radiotherapy		
Pharmacy available in my center able to mix chemotherapy timeously	12	92
Pediatric oncology doctors mix the chemotherapy themselves	1	8
ABVD available nearly 100% of the time	13	100
COPDac available nearly 100% of the time	13	100
Involved node radiation available	1	8
Involved field radiation available	12	92

The study objective of comparing interim PET-CT response with alterations in blood tests required a minimum of 42 patients with datasets including PET-CT at diagnosis and interim assessment, paired with blood results. At the time of writing, 114 participants had been enrolled and 70 appropriate data sets were available. No patients declined to

participate in the study, and all patients who were eligible for the study had been enrolled, although data capture was incomplete due to resource and time constraints.

Barriers

The funding sourced through formal channels required more time than anticipated to manage, due to a lack of familiarity with the process and restricted timelines set by some funders. (See [Table 3](#)) For example, one grant required the funding to be used within a four-month period, while another which was intended to supplement income for data capturers in each pediatric oncology unit could not be used for this purpose due to lack of time and capacity to manage the administrative requirements. For this reason, crowdfunding using sponsored sporting events was used to source funding that did not require stringent administrative oversights but still conformed to Wits University financial compliance criteria.

Discussion

Although a majority of childhood cancer research in Africa originates from a limited number of countries, including South Africa, there is minimal prospective research in this country, with most published manuscripts based on retrospective work.¹² Clinicians in South Africa thus rely on trials designed and implemented in high-income settings, which may not be appropriate for this patient population. This is the first South African study that has achieved involvement by all eligible pediatric oncology units, including enrollment, completion of treatment and publication of results.

This feasibility study determined whether a multicenter, harmonized management algorithm for pediatric and adolescent HL could successfully be implemented in all 14 South African state pediatric oncology units. Over the course of two years, the majority of participants reported access to the necessary diagnostic and therapeutic modalities required to participate.

The InPOG-HL-15-01 trial was the first collaborative multicenter prospective clinical trial for children with cancer in India.¹³ This four-year trial accrued 410 patients onto a simple study protocol with an ABVD backbone, with interim assessment after two cycles. Our study protocol follows a similar design, incorporating more intensive chemotherapy (COPDac) for high-risk patients. Challenges in the Indian study included variation in the timing of the first interim assessment imaging, restricted access to PET-CT and radiotherapy, and disagreement about radiotherapy indications, fields and doses. Over the course of the trial, this became more homogenous. Some centers required multiple reminders to input data timeously as they were more accustomed to retrospective studies.¹³ These factors are mirrored in our study, demonstrating similar challenges.

No patients declined to participate in this study which is an encouragement to clinician-researchers in this setting. Under-representation of children of African ancestry in clinical trials is a concern¹⁴ and does not engender confidence in clinicians who do not see their patient populations represented in published reports and treatment guidelines emanating from high-income settings. Studies such as the SACCSG-HL-2018 are thus vital to generate setting-specific data for African patients.

Barriers to full participation

While absence of a comprehensive database and small sample sizes are barriers to running clinical trials in the pediatric oncology field in the North American setting,¹⁵ this did not emerge as a barrier to this study, which is observational rather than experimental. Treatment represents standard of care, which may contribute to the high rate of patient participation.

Unwieldy regulatory requirements prohibited timely participation by many centers, with some centers taking more than 18 months to obtain approval. The stringent requirements of the multiple ethics and scientific committees assisted in the commitment to research governance, ie, improving belief in the project by ensuring that it was high quality, safe and ethical. However, the extremely long time frames of some of the ethics committees meant that patients were lost to recruitment. Although reciprocal approval across different HRECs was theoretically in place, this did not occur in reality. Having had the benefit of a few years running this study, it now appears that the more prudent course may have been to have each pediatric oncology unit submit their own HREC application which may have tested the commitment of the pediatric oncology units to participate. A systemic solution could include centralization of ethics committees to streamline the process.

Time constraints and understaffing are prominent concerns of many participants. As more South African multicenter, investigator-led studies are launched, it may become possible to co-fund additional staff to assist with administrative support, data capture and research coordination. While it is unlikely that research grants will be sufficient to pay for full salaries across the 14 sites, it may be possible to partially fund part-time staff members. South Africa's gross expenditure on research and development fell from a high of 0.95% of GDP in 2016¹⁶ to 0.75% of GDP in 2019, according to the latest survey on research intensity.¹⁷ Funding is thus becoming more difficult to source, due to factors such as the 2018 recession and the redirection of research funds to studies related to COVID-19. Currently, more funding is being sourced to support the study, and efforts to raise money through crowdfunding are ongoing.

Similar to the South African experience, barriers to conducting multicenter clinical trials in Africa include insufficient funding and staffing, lack of research environment, ethical and regulatory impediments.¹⁸ The recommended number of pediatric oncologists to annual new patients is 1:15 or 1:25¹⁹; Holton and most participants in this study reported much higher patient numbers than recommended (Table 1). Lack of familiarity with grant writing and management in LMICs means that, even when funding is available, it may not always be utilized most effectively.²⁰ Training and support may increase the effective use of these limited resources.

The protocol violations found on interim assessment are valuable lessons in conducting investigator-led trials in this setting. Without the intensive funding and human resources available in multicenter pharma-sponsored trials, the same level of attention to detail as found in these studies is not possible in the LMIC setting. However, studies such as these are more reflective of real-life medical practice compared with sponsor-led trials with stricter inclusion and exclusion criteria. The study findings are more representative of the pediatric and adolescent HL population in UMICs, with the notable

inclusion of patients with HIV infection. The impact of substituting agents is unknown but will be evaluated as part of the study outcomes.

The COVID-19 pandemic was an increased stress on participants but did not appear to have affected site induction or recruitment significantly, although it may have affected the time to regulatory approval as ethics committees were inundated with requests to approve studies related to the pandemic.

Facilitators

Before this project was initiated, management regimens included intensive regimens with high toxicity requiring hospital admissions.⁶ Adopting less toxic regimens may decrease treatment abandonment as there is increased convenience, lower morbidity and lower cost.²¹ Such costs would include out-of-pocket expenses as the majority of pediatric oncology care is state-subsidized. These potential benefits may contribute to the commitment of the study participants to collaborate in this harmonization project and may help to improve the survival rate. Further enablers which could be exploited in future studies include regular communication, a simple management algorithm, free online data collection tool and research support from a national coordinator.

Facilitators include commitment to contributing to African research, improving patient outcomes, simple data collection process, team interaction, career advancement, improved training of researchers, financial and logistical support.²² These factors are not isolated to childhood cancer research. A streamlined, centralized ethics review process to assist clinician-researchers with limited time and experience could also be beneficial.

Achieving the Sustainable Development Goals (SDG), a blueprint for global progress, requires concerted efforts to strengthen research capacity in LMIC. The SDG recognize research capacity as essential to the generation of novel, locally relevant knowledge to deliver appropriate services to prevent and control disease and suffering.²³ Projects such as SACCSG-HL-2018, which aims to create a locally relevant evidence base for the treatment of HL in South Africa, address this mandate closely, and are thus crucial to develop and support.

Growing concerns about local research agendas being set by researchers from HIC²⁴ indicate that South African institutions should strengthen research capacity and set locally relevant priorities to mitigate this.

Recommendations

A formal research training program may enable successful investigator-led clinical trials. Such training should include grant writing and management, recruitment and retention of study participants, research coordination and collaborative publishing. Protected time for research is essential. Funding is required to employ research and administrative support staff as clinicians who do not have sufficient time to participate fully. Research should be given greater priority to improve survival rates and ethics review processes should be streamlined.

Limitations

Before starting recruitment of sites, it might have been prudent to run a formal assessment of staff needs and workload such as the ASCO Clinical Trial Workload Assessment Tool²⁵ or the King's College NHS Feasibility checklist,²⁶ although these are tailored for high-income settings and there are no published similar tools in Africa.

Conclusion

Despite the obvious obstacles to conducting research in a resource-constrained setting, this study demonstrates that multicenter collaboration is achievable. The protocol described here represents an ATR suitable for a MIC setting, and harmonization of pediatric and adolescent HL treatment in this format is feasible in South Africa: the minimum requirements are available in the majority of centers, and clinicians are committed to the process. Minimal funding is required to initiate such a project, but full participation to run high-quality studies may require more financial investment. Focused funding and increased prioritization of research may address systemic barriers to full participation.

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ORCID

Jennifer Geel  <http://orcid.org/0000-0001-8792-3251>
 Marc Hendricks  <http://orcid.org/0000-0002-3636-0994>
 Yasmin Goga  <http://orcid.org/0000-0002-6740-2376>
 Beverley Neethling  <http://orcid.org/0000-0002-7580-8042>
 Vutshilo Netshituni  <http://orcid.org/0000-0003-2169-6038>
 Johani Vermeulen  <http://orcid.org/0000-0003-1180-6862>
 Anel van Zyl  <http://orcid.org/0000-0003-3370-0874>
 Fareed Omar  <http://orcid.org/0000-0002-2319-1087>
 Jan du Plessis  <http://orcid.org/0000-0002-1914-4202>
 Thandeka Ngcana  <http://orcid.org/0000-0003-4802-6317>
 Daynia E. Ballot  <http://orcid.org/0000-0003-4985-048X>
 Monika L. Metzger  <http://orcid.org/0000-0002-7102-4611>

References

1. Gatta G, Botta L, Rossi S, et al. Childhood cancer survival in Europe 1999–2007: results of EUROCARE-5-a population-based study. *Lancet Oncol*. 2014;15(1):35–47. doi:10.1016/S1470-2045(13)70548-5.
2. Mauz-Körholz C, Metzger ML, Kelly KM, et al. Pediatric Hodgkin lymphoma. *J Clin Oncol*. 2015;33(27):2975–2985. doi:10.1200/JCO.2014.59.4853.
3. Bazzeh F, Rihani R, Howard S, Sultan I. Comparing adult and pediatric Hodgkin lymphoma in the surveillance, epidemiology and end results program, 1988–2005: an analysis of 21734 cases. *Leuk Lymphoma*. 2010;51(12):2198–2207. doi:10.3109/10428194.2010.525724.
4. Howard SC, Ortiz R, Baez LF, et al. Protocol-based treatment for children with cancer in low income countries in Latin America a report on the recent meetings of the Monza International School of Pediatric Hematology/Oncology (MISPHO)—part II. *Pediatr Blood Cancer*. 2007;48(4):486–490. doi:10.1002/pbc.20989.
5. Rossig C, Juergens H, Schrappe M, et al. Effective Childhood cancer treatment: the impact of large scale clinical trials in Germany and Austria. *Pediatr Blood Cancer*. 2013;60(10):1574–1581. doi:10.1002/pbc.24598.
6. Geel JA, Chirwa TC, Rowe B, et al. Treatment outcomes of children with Hodgkin lymphoma between 2000 and 2010: first report by the South African Children's cancer study group. *Pediatr Blood Cancer*. 2017;64(10):e26536. doi:10.1002/pbc.26536.
7. Chung KC, Song JW, Grewal R, et al. A guide on organizing a multicenter clinical trial: the WRIST study group. *Plast Reconstr Surg Au*. 2011;126(2):515–523.
8. Cuccaro A, Annunziata S, Cupelli E, et al. TARC levels predict response in Hodgkin lymphoma. *Cancer Med*. 2016;5(3):398–406. doi:10.1002/cam4.585.
9. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. *Journal of Biomedical Informatics*. 2009 Apr;42(2):377–381.
10. ICMJE Recommendations: Defining the Role of Authors and Contributors [Internet]. [cited 2021 Jul 25]. Available from: <http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html>.
11. Geel JA, Myezo K, Hendricks M, et al. Multicentre national clinical research in the LMIC setting. Can south africa produce quality cancer research? Poster session: 52nd Congress of the International Society of Paediatric Oncology (SIOP) Virtual Congress, October 14–17, 2020. *Pediatr Blood Cancer*. 2020;67(Suppl. 4):e28742. p 370.
12. van Heerden J, Zaghoul M, Neven A, et al. JCO Global Oncology Pediatric oncology clinical trials and collaborative research in Africa: current landscape and future perspectives. *JCO Glob Oncol*. 2020;6:1264–1275. doi:10.1200/GO.20.00159.
13. Arora RS, Mahajan A, Dinand V, et al. InPOG-HL-15-01 – challenges and lessons learnt in setting up the first collaborative multicentre prospective clinical trial in childhood cancer in India. *Pedia Hemato Oncol J*. 2020;5(4):166–170. doi:10.1016/j.phoj.2020.02.001.
14. Kizub D, Manner CK, Graef K, et al. Cancer Prevention and Control Special Articles. Action for increasing diversity, market access, and capacity in oncology registration trials – is Africa the answer? Report from a satellite session of the accelerating anti-cancer agent development and validation workshop [Internet]. Vol. 8, JCO Global Oncol. 2022. Available from: <https://ascopubs.org/go/authors/open-access>.
15. Hauck CL, Cartmell KB, Mueller M, Kelechi TJ. Scoping review: barriers and facilitators to enrollment in pediatric. *Oncol Clin Trial. Pedia Nurs*. 2021;47(2):79–96.
16. Bernstein E. 2016. Global R&D Funding Forecast. Reference guide creating innovation leadership solutions message from the IRI President 2016 GLOBAL R&D FUNDING FORECAST CONTENTS. 2016.
17. van der Merwe C. South African research intensity plummets – Research Professional News [Internet]. Research Professional News. 2021 [cited 2021 Apr 5]. Available from: <https://www.researchprofessionalnews.com/rr-news-africa-south-2021-2-south-african-research-spending-plummets/>.

18. Alemayehu C, Mitchell G, Nikles J. Barriers for conducting clinical trials in developing countries – a systematic review. *Int J Equity Health*. 2018;17(1):1–11. doi:[10.1186/s12939-018-0748-6](https://doi.org/10.1186/s12939-018-0748-6).
19. Halton JM, Hand J, Byron P, Strother D. Establishing Physician to Patient Ratios and Predicting Workforce Needs for Canadian Pediatric Hematology-Oncology Programs. *Pediatr Blood Cancer*. 2013;60:564–569.
20. The Academy of Medical Science TIP. Strengthening clinical research capacity in low- and middle-income countries. Workshop report. 3–4 July 2017 London, United Kingdom. 2017.
21. Jain S, Kapoor G, Bajpai R. ABVD-based therapy for hodgkin lymphoma in children and adolescents: lessons learnt in a tertiary care oncology center in a developing country. *Pediatr Blood Cancer*. 2016;63(6):1024–1030. doi:[10.1002/pbc.25935](https://doi.org/10.1002/pbc.25935).
22. Conradie A, Duys R, Forget P, Biccard BM. Barriers to clinical research in Africa: a quantitative and qualitative survey of clinical researchers in 27 African countries. *Br J Anaesth*. 2018;121(4):813–821. doi:[10.1016/j.bja.2018.06.013](https://doi.org/10.1016/j.bja.2018.06.013).
23. United Nations. Transforming our world: the 2030 agenda for sustainable development A/RES/70/1 [Internet]. United Nations General Assembly. 2016. Available from: <https://sustainabledevelopment.un.org/content/documents/21252030>. Agenda for Sustainable Development web.pdf
24. Izugbara CO, Kabiru CW, Amendah D, et al. “It takes more than a fellowship program”: Reflections on capacity strengthening for health systems research in sub-Saharan Africa. *BMC Health Serv Res*. 2017;17(S2):1–5. doi:[10.1186/s12913-017-2638-9](https://doi.org/10.1186/s12913-017-2638-9).
25. Good MJ, Hurley P, Woo KM, et al. Assessing clinical trial-associated workload in community-based research programs using the ASCO clinical trial workload assessment tool. *J Oncol Pract*. 2016;12(5):e536–47–e547. doi:[10.1200/JOP.2015.008920](https://doi.org/10.1200/JOP.2015.008920).
26. Feasibility and Review Process – King’s College Hospital NHS Foundation Trust [Internet]. [cited 2022 Jan 2]. Available from: <https://www.kch.nhs.uk/research/setting-up/feasibility-and-review-process>

Chapter 5. Improved survival 2022

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RESEARCH ARTICLE

Improved survival of children and adolescents with classical Hodgkin lymphoma treated on a harmonised protocol in South Africa

Jennifer Geel¹  | Anel van Zyl²  | Jan du Plessis³  | Marc Hendricks⁴  |
Yasmin Goga⁴  | Amy Carr⁵  | Beverley Neethling⁶  | Artsiom Hramyka⁷  |
Fareed Omar⁸  | Rema Mathew⁹  | Lizette Louw¹⁰  | Thanushree Naidoo^{11,12} |
Thandeka Ngcana¹³  | Tanya Schickerling¹⁴  | Vutshilo Netshituni¹⁵  |
Elelwani Madzhia¹⁶ | Liezl du Plessis¹⁷  | Tom Kelsey⁷  | Daynia E. Ballot¹⁸  |
Monika L. Metzger¹⁹ 

¹Pediatric Haematology-Oncology, University of the Witwatersrand, Charlotte Maxeke Johannesburg Academic Hospital, Wits Donald Gordon Medical Centre, Johannesburg, South Africa

²Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Tygerberg Hospital, Cape Town, South Africa

³Pediatric Haematology-Oncology, University of the Free State, Universitas Hospital, Bloemfontein, South Africa

⁴Department of Paediatrics and Child Health, Haematology-Oncology Service, Faculty of Health Sciences, University of Cape Town, Red Cross War Memorial Children's Hospital, Cape Town, South Africa

⁵Pediatric Haematology-Oncology, University of KwaZulu-Natal Durban, Greys Hospital, Pietermaritzburg, South Africa

⁶Pediatric Haematology-Oncology, University of KwaZulu-Natal Durban, Inkosi Albert Luthuli Hospital and Greys Hospital, Pietermaritzburg, South Africa

⁷School of Computer Science, University of St Andrews, St Andrews, UK

⁸Pediatric Haematology-Oncology, University of Pretoria, Steve Biko Academic Hospital, Pretoria, South Africa

⁹Pediatric Haematology-Oncology, Walter Sisulu University, Frere Hospital, East London, South Africa

¹⁰Centre of Molecular Imaging and Theranostics, Johannesburg, South Africa

¹¹Department of Radiation Oncology, University of the Witwatersrand, Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg, South Africa

¹²Wits Donald Gordon Medical Centre, Johannesburg, South Africa

¹³Pediatric Haematology-Oncology, University of the Witwatersrand, Chris Hani Baragwanath Academic Hospital, Wits Donald Gordon Medical Centre, Johannesburg, South Africa

¹⁴Netcare Alberton Hospital, Johannesburg, South Africa

¹⁵Pediatric Haematology-Oncology, University of Limpopo, Polokwane-Mankweng Hospital Complex, Polokwane, South Africa

¹⁶Pediatric Haematology-Oncology, Sefako Makgatho University, Dr George Mukhari Hospital, Garankuwa, South Africa

¹⁷Pediatric Haematology-Oncology, University of the Free State, Kimberley Hospital, Kimberley, South Africa

¹⁸School of Clinical Medicine, University of the Witwatersrand, Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg, South Africa

¹⁹Medecins sans Frontieres, Geneva, Switzerland

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; ABVD-ChlVPP, doxorubicin, bleomycin, vinblastine, dacarbazine-chlorambucil, vinblastine, prednisone and procarbazine; ATR, adapted treatment regimen; CHIPS, Childhood Hodgkin International Prognostic Score; COPDac, cyclophosphamide, vincristine, prednisone, dacarbazine; CT, computed tomography; DS, Deauville score; GICC, Global Initiative for Childhood Cancer; HIC, high-income country; HIV, human immunodeficiency virus; HL, Hodgkin lymphoma; LMIC, low- and middle-income country; OPPO/OEPA-COPP, vincristine, procarbazine/etoposide, prednisone and doxorubicin; OS, overall survival; PET-CT, positron emission tomography-computed tomography; PI, principal investigator; POU, paediatric oncology unit; RER, rapid early response; SER, slow early response.

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Correspondence

Tom Kelsey, School of Computer Science,
University of St Andrews, St Andrews, KY16
9AJ, UK.

Email: twk@st-andrews.ac.uk

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Abstract

Background: Historic South African 5-year overall survival (OS) rates for Hodgkin lymphoma (HL) from 2000 to 2010 were 46% and 84% for human immunodeficiency virus (HIV)-positive and HIV-negative children, respectively. We investigated whether a harmonised treatment protocol using risk stratification and response-adapted therapy could increase the OS of childhood and adolescent HL.

Methods: Seventeen units prospectively enrolled patients less than 18 years, newly diagnosed with classical HL onto a risk-stratified, response-adapted treatment protocol from July 2016 to December 2022. Low- and intermediate-risk patients received four and six courses of adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD), respectively. High-risk patients received two courses of ABVD, followed by four courses of cyclophosphamide, vincristine, prednisone, and dacarbazine (COPDac). Those with a slow early response and bulky disease received consolidation radiotherapy. HIV-positive patients could receive granulocyte colony-stimulating factor and less intensive therapy if stratified as high risk, at the treating clinician's discretion. Kaplan–Meier survival analysis was performed to determine 2-year OS and Cox regression to elucidate prognostic factors.

Results: The cohort comprised 132 patients (19 HIV-positive, 113 HIV-negative), median age of 9.7 years, with a median follow-up of 2.2 years. Risk grouping comprised nine (7%) low risk, 36 (27%) intermediate risk and 87 (66%) high risk, with 71 (54%) rapid early responders and 45 (34%) slow early responders, and 16 (12%) undocumented. Two-year OS was 100% for low-risk, 93% for intermediate-risk, and 91% for high-risk patients. OS for HIV-negative (93%) and HIV-positive (89%) patients were similar ($p = .53$). Absolute lymphocyte count greater than 0.6×10^9 predicted survival (94% vs. 83%, $p = .02$).

Conclusion: In the first South African harmonised HL treatment protocol, risk stratification correlated with prognosis. Two-year OS of HIV-positive and HIV-negative patients improved since 2010, partially ascribed to standardised treatment and increased supportive care. This improved survival strengthens the harmonisation movement and gives hope that South Africa will achieve the WHO Global Initiative for Childhood Cancer goals.

KEYWORDS

adolescent, child, GICC, harmonisation, Hodgkin lymphoma, South Africa

1 | INTRODUCTION

Retrospective reports have documented relatively high survival rates for paediatric Hodgkin lymphoma (HL) with 85% 3-year overall survival (OS) in Morocco¹ and 96% 5-year OS in Egypt,² both lower middle-income countries. There are minimal prospective data on HL survival in Africa, and hardly any data on children with human immunodeficiency virus (HIV). Standardised HL guidelines have been shown to improve survival.³ However, these guidelines are frequently used without adaptation in low- and middle-income countries (LMIC) despite being created for use in high-income countries (HIC) with adequate access

to excellent supportive care, and various salvage therapy options, such as antibody–drug conjugates, checkpoint inhibitors and stem cell transplantation.

The WHO Global Initiative for Childhood Cancer (GICC) focuses on six index cancers, including HL.⁴ In 2014, the South African Children's Cancer Study Group (SACCSG) initiated a process to harmonise diagnostic and treatment guidelines for childhood cancers, starting with HL. Prior to this initiative, risk grouping was not widely applied, and response-adapted therapy was not widely practised. A multicentre, retrospective study documented that the 5-year OS rates for children with HL were low at 46% for those

with HIV, compared to 84% for those without, and that treatment with doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) yielded higher survival rates than vincristine, procarbazine/etoposide, prednisone and doxorubicin-cyclophosphamide, vincristine, prednisone, procarbazine (OPPA/OEPA-COPP) and adriamycin, bleomycin, vincristine and dacarbazine-chlorambucil, vinblastine, prednisone and procarbazine (ABVD-ChIVPP). The strongest prognosticators were HIV infection and advanced disease, thus informing the treatment choices for patients in the prospective treatment protocol.⁵

The current prospective study aimed to determine if a harmonised treatment protocol incorporating risk stratification and response adjustment, representing an adapted treatment regimen (ATR) for an upper middle-income country, was associated with improved survival, and to further evaluate potential prognostic markers of survival.

2 | METHODS

2.1 | Setting

South Africa, an upper middle-income country, has a high rate of unemployment, the highest number of HIV-positive people in the world and sustained inequity, with a documented childhood cancer OS of approximately 60%.^{6,7} Patients are treated in 12 state-sector academic hospitals and five private-sector hospitals. State hospitals provide subsidised treatment based on means assessment. Patients under 6 years, refugees, those receiving state financial grants and those with no income were fully subsidised by the state (H0). Three higher levels of income classification (H1–H3) reflected varying degrees of state subsidisation, while foreign nationals who did not have official refugee status and patients with medical insurance were grouped in the highest income classification (private) with no subsidisation.⁸

2.2 | Inclusion and exclusion criteria

This multicentre, prospective, observational study included newly diagnosed, treatment-naïve patients under 18 years with histologically confirmed classical HL diagnosed and treated in South Africa from July 2016 to December 2022. Exclusion criteria included nodular lymphocyte-predominant HL, previous treatment for HL, those who died before treatment was initiated and those with substantively incomplete data collection.

2.3 | Staging and imaging

Patients were staged according to the Ann Arbor classification system and risk-stratified into low, intermediate or high risk (Table S1). This risk stratification was based on various treatment algorithms in

use³ and was intended to ensure that children with HL in South Africa receive appropriate treatment.

Staging investigations included chest x-ray, fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT), or computed tomography when PET-CT not available and bone marrow trephine biopsy for all patients. Bulky disease was defined as peripheral lymph nodes or lymph node aggregates greater than 6 cm in any axis, or mediastinal adenopathy greater than 33% of the thoracic diameter in an anteroposterior chest radiograph. Central review of PET-CT was performed as requested. Laboratory investigations included haematological (total white cell count, absolute lymphocyte count (ALC), absolute eosinophil count, haemoglobin), non-specific markers (ferritin, lactate dehydrogenase [LDH], albumin, erythrocyte sedimentation rate [ESR]) and HIV status. Pre-treatment echocardiograms were performed according to availability.

2.4 | Intervention

Patients were enrolled in a risk-stratified, response-adapted protocol comprising two cycles of ABVD for all patients, followed by interim assessment. Based on treatment response, further treatment included: two further cycles of ABVD for low-risk patients, four cycles of ABVD for intermediate-risk patients and four cycles of COPDac (cyclophosphamide, vincristine, prednisone, dacarbazine) for high-risk patients.⁹

2.5 | Definitions of response

Response evaluation was based on the 2015 revised Lugano classification,¹⁰ and was determined at response evaluation after two to three cycles of ABVD. In patients who did not have PET-CT performed, CT was considered sufficient. Rapid early response (RER) was defined as complete resolution (CR) of measurable disease and resolution of PET avidity, that is, Deauville score (DS) 1, 2 or 3 or a good partial response (GPR) with a reduction of 50% or greater in any one axis of a measurable nodal mass with a DS of 1–3.¹¹

Slow early response (SER) was defined as a partial response (PR) with shrinkage of measurable disease not achieving 50% reduction in any one axis or DS 4 or 5. Progressive disease (PD) was defined as increased intensity of FDG uptake on the PET-CT from baseline, any increase in any one axis of a measurable nodal mass and/or new lesions. Stable (refractory) disease was defined as DS 4 or 5, or less than 50% decrease from baseline in the sum of the product of the perpendicular diameters (SPD) for multiple lesions of up to six dominant measurable nodes and extranodal sites.¹¹ Progressive disease was defined as DS of 4 or 5 with increased intensity from baseline, increase by 50% or higher size from the nadir, or significantly increased, new, or recurrent splenomegaly with focal lesions on available radiology images.

2.6 | Permitted protocol modifications

HIV-positive patients could receive additional support with granulocyte colony-stimulating factor, and could be treated on less intensive therapy (intermediate risk instead of high risk), at the treating clinician's discretion. Patients with pre-existing cardiac dysfunction (ejection fraction of <50%) could be treated with COPDac instead of ABVD upfront, have doxorubicin omitted or epidoxorubicin substituted for doxorubicin if available, at the discretion of the treating clinical team.

2.7 | Consolidation with radiotherapy

Radiotherapy was limited to those sites in which functional activity (DS 4 to 5) was appreciable at response evaluation and for mediastinal masses greater than 33% of the intrathoracic diameter at presentation, regardless of the response evaluation. Bulky disease outside the mediastinum at presentation did not mandate radiation, if there was no FDG uptake on the interim PET-CT scan (DS 1–3). For patients who did not have PET-CT, only mediastinal sites and nodal masses classified as SER with a partial response as defined above were irradiated. Involved site radiotherapy utilising three-dimensional conformal radiotherapy planning or involved field radiation was administered according to institutional capacity at a dose of 21–25 Gy, in either 1.5 or 1.8 Gy fractions.

2.8 | Statistics

The primary study endpoints were 2-year progression-free survival (PFS) and OS. OS was defined as time from diagnosis to death from any cause. PFS was defined as time from diagnosis to date of confirmation of relapsed or refractory disease. Persistent disease identified within 90 days of completion of therapy was deemed refractory; disease that returned more than 90 days after therapy was classified as early relapse if within 12 months from the end of therapy, and late relapse if thereafter. Patients who did not experience an event were censored at the date of the last follow-up.

Data were entered prospectively into a central REDCap¹² database by one clinician-researcher from each paediatric oncology unit (POU), and the principal investigator (PI) managed the entire database. Data were frozen on 31 December 2022. The Kaplan-Meier method and log-rank test were used to calculate survival analysis. A Cox proportional hazards model was used for univariate analysis to identify predictive factors for OS. Potential prognostic factors included demographic (age, sex, maternal education and hospital-assigned financial classification), disease-specific (HIV infection, histological subtype, B symptoms, mediastinal mass, pleural effusion, stage, risk group), haematological (total white cell count, ALC, total eosinophil count, haemoglobin), non-specific markers (LDH, ESR, ferritin, albumin) and Childhood Hodgkin International Prognostic Score (CHIPS).¹³ These

non-specific markers were evaluated in an attempt to find prognostic markers that are relatively cheap and widely available in South Africa. In the CHIPS score, one point was assigned for each of the four known predictors of adverse event-free survival (EFS): stage 4, large mediastinal mass, fever and albumin less than 35 g/dL.

Treatment abandonment was defined as failure to complete curative treatment, while loss to follow-up was defined as any patient who did not return for follow-up appointments for 1 year and was unreachable despite efforts to contact the family. Abandonment and loss to follow-up were censored in the survival curves. A *p*-value of less than .05 was considered statistically significant. The whole cohort was analysed together, and the HIV-uninfected patients were analysed separately to limit confounders.

2.9 | Ethics

The study was approved by the University of the Witwatersrand human research ethics committee (M1711100) and registered on the National Health Research Database and the seven Provincial Health Research Databases in which POUs were located. Approval was obtained from the ethics committee of each participating POU by the national PI.

3 | RESULTS

In total, 142 cases of HL were identified, of which 10 were excluded (Figure 1). The majority of patients (*n* = 72; 55%) were younger than 10 years of age. The median age at presentation in 113 (86%) HIV-negative patients was 9.7 years (range 2.3–18.7 years), and 9.1 years (range 4.8–18.2) in 19 (17%) HIV-positive patients, with a male predominance in both groups. The median follow-up time was 2.2 years (range: 0–7.5 years). Fifteen HIV-positive patients (79%) were already receiving antiretroviral therapy at the time of diagnosis of HL, and nine (60%) of these had undetectable viral loads. The majority (*n* = 106; 80%) received full or heavily subsidised care, and 16 (12%) patients were treated in the private sector (Table 1). The most common histological subtype was nodular sclerosing (*n* = 67; 51%), followed by mixed cellularity (*n* = 38; 29%). Histological subtype was not determined in 23 patients (17%), the majority, because these patients were too ill at presentation to undergo lymph node excision. Most patients presented with Ann Arbor stage 3 and 4 disease (*n* = 87; 66%), while 84 patients (64%) presented with B symptoms, 66 (50%) with bulky disease, and 40 (30%) patients with a mediastinal mass. The majority (*n* = 87; 66%) had high-risk disease, 36 (27%) had intermediate-risk disease and nine patients (7%) had low-risk disease. Demographic data and disease characteristics at diagnosis are shown in Table 1.

Ten patients (7.6%) presented with autoimmune manifestations including immune thrombocytopenia (*n* = 2; 1.5%), autoimmune

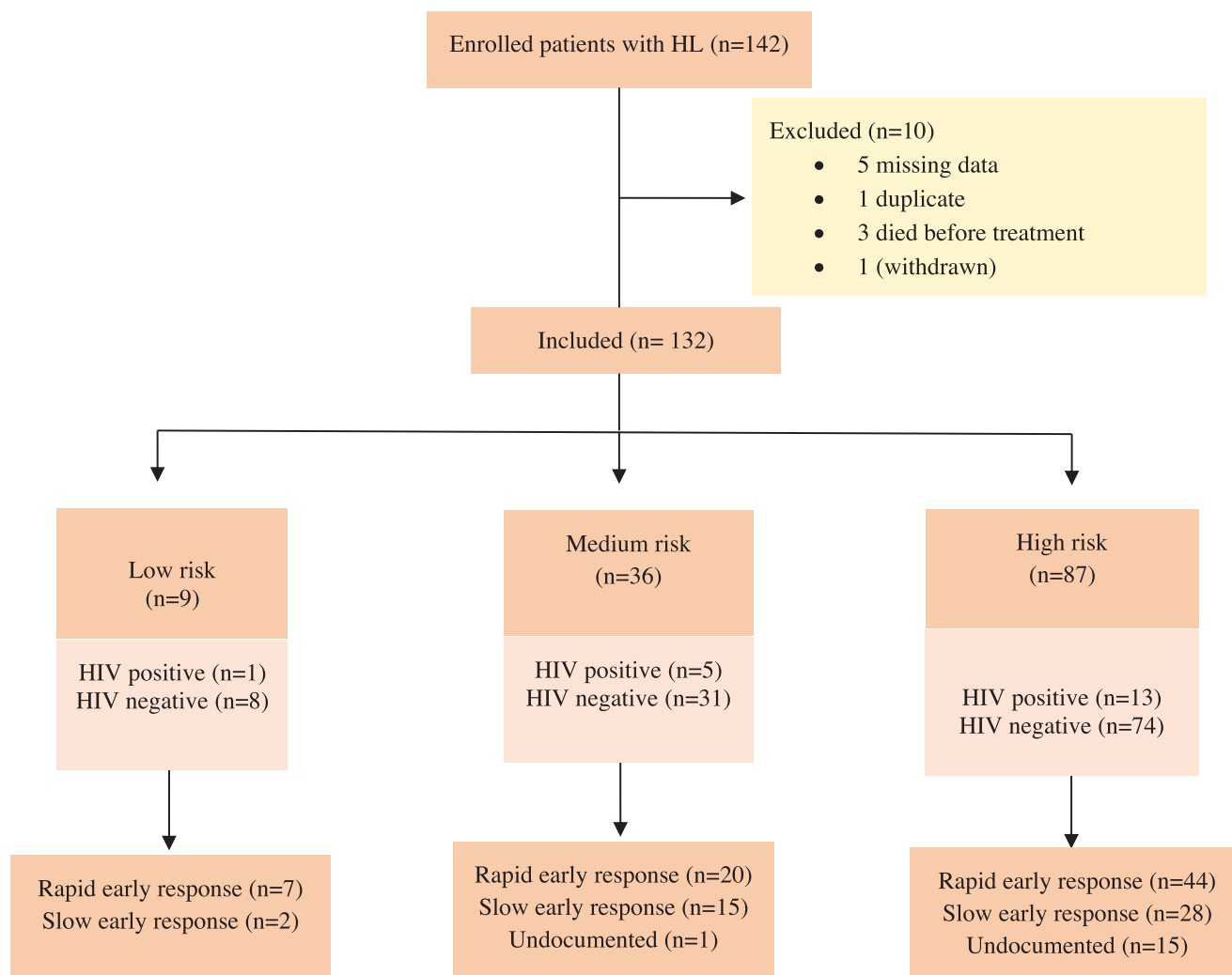


FIGURE 1 Enrolment, risk stratification and response assessment of children and adolescents on SACCSG (South African Childhood Cancer Study Group)-HL 2018.

haemolytic anaemia ($n = 7$; 5.3%), and Guillain-Barré syndrome ($n = 1$; 0.8%), while four (4.1%) HIV-negative patients of the 98 patients who had echocardiograms performed had cardiac dysfunction prior to starting therapy.

3.1 | Protocol deviations

Seven high-risk patients were undertreated (ABVD only instead of ABVD and COPDac), one intermediate-risk patient was overtreated (COPDac instead of ABVD) and three low-risk patients were overtreated (six cycles of ABVD instead of four).

3.2 | Response evaluation

Response evaluation was performed in 114 patients (86%): 104/114 (91%) with PET-CT scans and 10/114 (9%) with CT. Of 18 patients who

did not have response evaluation performed, four died before reaching this point, four abandoned therapy, and two have not yet completed treatment. In six cases, no reason was documented. Seventy-three (65%) were classified as RER, 44 (39%) as SER and 15 were undocumented (see Figure 1).

3.3 | Radiation

Based on SER or the presence of bulky large mediastinal adenopathy at presentation, radiotherapy was indicated in 61 (46%) patients. Of these, 36 (59%) received radiation as mandated by the protocol. Reasons for omission included failure to adhere to the protocol due to poor understanding ($n = 11$), treatment abandonment ($n = 5$), refusal by the local radiation oncologist ($n = 3$), progressive disease with the decision to administer more chemotherapy ($n = 2$), inconclusive PET-CT results ($n = 2$), clinical judgement based on previous toxicity ($n = 1$) and death ($n = 1$).

TABLE 1 Patient characteristics and univariate analysis of potential prognostic factors.

	Variable	HIV (–) n = 113	%	HIV (+) n = 19	%	Total cohort n = 132	%	2-year OS	p-Value
Age	<10 years	50	56	17	89	72	55	92	.96
	>10 years	63	44	2	11	60	45	93	
Maternal education	Tertiary	18	16	0	0	18	14	100	.32
	School (any)	52	46	12	63	64	49	93	
	Undocumented	43	38	7	37	50	38	90	
Hospital financial classification	Private sector	15	13	1	5	16	12	100	.11
	H0, H1	81	72	0	0	99	75	94	
	H2, H3	17	15	18	95	17	13	78	
Histological subtype	Nodular sclerosing	58	51	9	47	67	51	90	.31
	Mixed cellularity	34	30	4	21	38	30	100	
	Lymphocyte depleted	2	2	0	0	2	1.5	100	
	Lymphocyte rich	2	2	0	0	2	1.5	100	
	NOS/undocumented	17	15	6	32	23	17	87	
EBER-ISH	Yes	41	36	4	21	47	36	93	.15
	No	25	19	6	32	31	23	100	
B symptoms	Present	72	64	12	63	84	64	93	.59
	Absent	41	36	7	3	48	36	92	
Ann Arbor stage	Stage 1	5	4	0	0	5	4	100	.45
	Stage 2	34	30	6	32	40	30	97	
	Stage 3	36	22	4	21	40	30	92	
	Stage 4	38	34	9	47	47	36	88	
Bulky disease (mediastinal and peripheral)	No	59	52	7	3	66	50	92	.69
	Yes	54	48	12	63	66	50	94	
Mediastinal mass (n = 113)	Yes	37		16	84	40	30	92	.88
	No	76	67	3	16	92	70	93	
Risk group	Low risk	8	7	1	5	9	7	100	.61
	Medium risk	31	27	5	26	36	27	94	
	High risk	74	66	13	68	87	66	91	
CHIPS	1	29	26	5	26	33	25	91	.64
	2	25	22	4	21	30	23	97	
	3	23	20	5	26	27	21	8	
	4	4	4	4	21	9	7	89	
	Undocumented	28	25	1	5	33	25	97	
Autoimmune manifestations	No	96	85	17	90	113	86	93	.1
	Yes	8	7	2	10	10	8	100	
	Undocumented	9	8	0	0	9	7	73	
Ferritin (n = 114)	<500 µg/L	59	62	9	47	68	60	97	.08
	>500 µg/L	37	39	9	47	46	40	88	

(Continues)

TABLE 1 (Continued)

	Variable	HIV (–) n = 113	%	HIV (+) n = 19	%	Total cohort n = 132	%	2-year OS	p-Value
Lactate dehydrogenase (n = 126)	<500 µg/L	85	79	16	84	101	80	93	.57
	>500 µg/L	23	21	2	10	25	20	96	
Erythrocyte sedimentation rate	<30 mm/h	29	26	3	16	32	24	90	.65
	>30 mm/h	57	50	11	58	68	52	93	
	Undocumented	27	24	5	26	32	24	96	
Total white cell count	<15 × 10 ⁹ /L	93	82	18	95	111	84	94	.13
	>15 × 10 ⁹ /L	20	18	1	5	21	16	84	
Absolute lymphocyte count (n = 130)	>0.6 × 10 ⁹ /L	107	96	15	79	122	94	94	.02
	<0.6 × 10 ⁹ /L	5	4	3	16	8	6	75	
Absolute eosinophil count (n = 130)	>0.6 × 10 ⁹ /L	16	14	2	10	18	14	100	.23
	<0.6 × 10 ⁹ /L	96	86	16	84	112	86	91	
Haemoglobin	>10.5 g/dL	55	49	5	26	60	46	95	.44
	<10.5 g/dL	58	51	14	74	72	54	91	
Albumin (n = 131)	>35 g/L	50	44	7	37	57	44	96	.19
	<35 g/L	63	56	11	58	74	56	90	

Abbreviations: CHIPS, Childhood Hodgkin International Prognostic Score; EBER-ISH, Epstein–Barr virus-encoded RNA in situ hybridisation.

TABLE 2 Distribution of treatment failures.

	High risk		Medium-risk	
	HIV+	HIV–	HIV+	HIV–
Refractory or progressive disease (n = 13)				
Histological confirmation	0	4	0	0
No histological confirmation	1	6	0	2
Early relapse (n = 3)				
Histological confirmation	1	1	0	1
No histological confirmation	0	0	0	0
Late relapse (n = 3)				
Histological confirmation	0	2	0	0
No histological confirmation	0	1	0	0

3.4 | Treatment failure

Thirteen (9.8%) patients were identified as having refractory disease, four with histological confirmation, while six patients were diagnosed with relapsed disease, five histologically confirmed. None were low risk at presentation, and the majority were HIV-negative (see Table 2). The remainder were considered to have refractory disease based on end-of-treatment PET-CT scans, despite this assessment not being recommended in the study protocol. Therefore, the treatment failure rate was between 7% (proven) and 14% (total). Patients with relapsed or refractory disease were treated off-protocol according to institutional

preference: eight patients received autologous stem cell transplants, and two were being prepared for transplant. At the last follow-up date, one patient had demised, six were alive in full remission and seven were alive with disease.

3.5 | Overall survival and progression-free survival

Causes of death included progression of disease (n = 1), relapse (n = 1), treatment-related mortality (n = 6) and other (n = 1). Five high-risk patients (4%) abandoned treatment after receiving two to four cycles

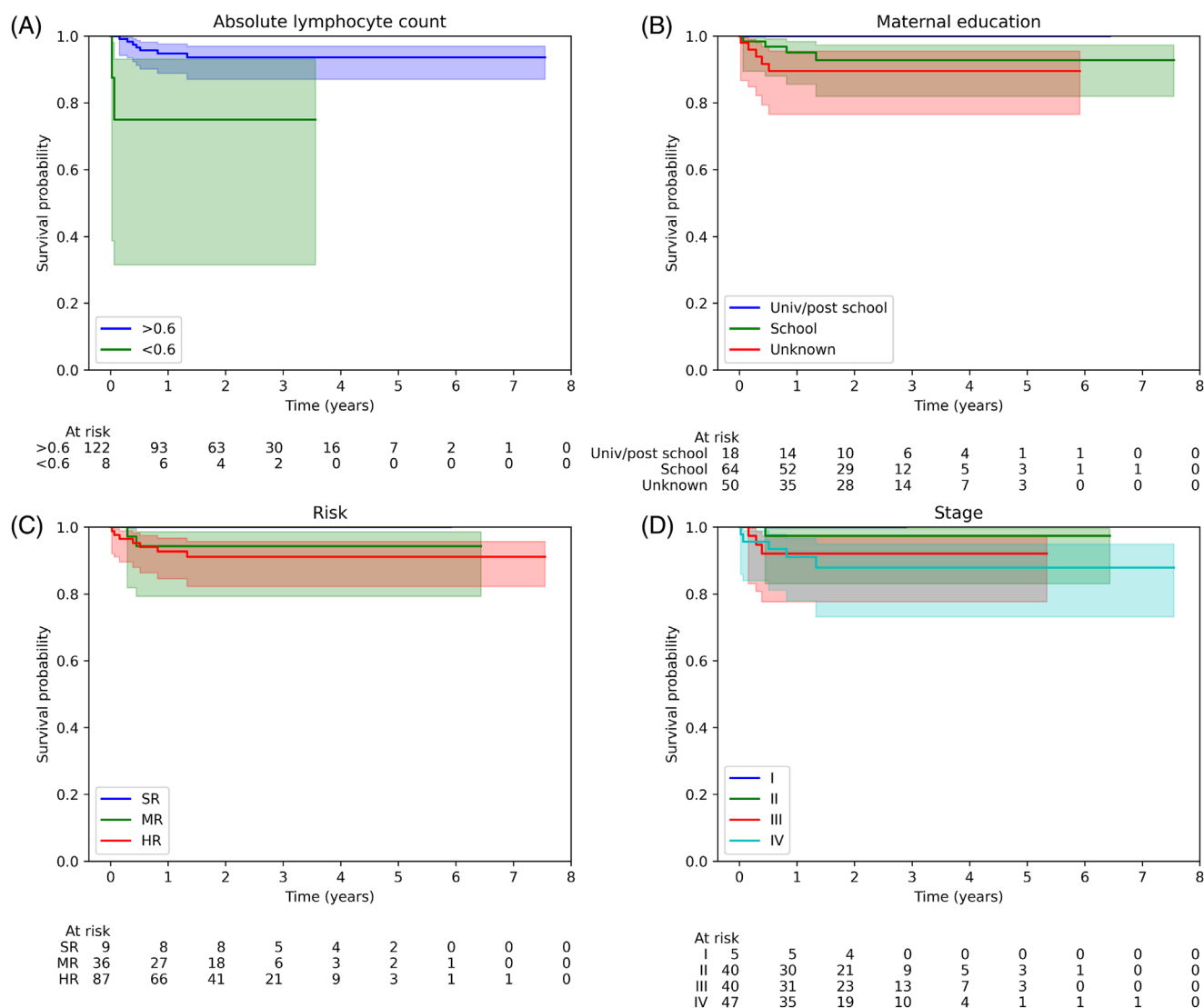


FIGURE 2 (A) Overall survival of current and historical cohort (B).

of chemotherapy, but were documented to be alive (47–941 days follow-up) despite not completing therapy.

The 2-year OS for the entire cohort was 92.6%, higher than that of the historical cohort, which was 84% ($p = .004$) (see Figure 2) with a PFS of 83%. HIV-negative patients had a 2-year OS of 93%, in comparison with 89% in the HIV-positive patients ($p = .53$). The 2-year OS was 100% for patients with stage 1 disease, 97% for stage 2, 92% for stage 3 and 88% for stage 4 ($p = .45$). The 2-year OS was 100% for low-risk, 94% for intermediate-risk, and 91% for high-risk patients ($p = .62$). The 2-year PFS for risk stratification was as follows: low risk 100%, intermediate risk 90% (95% confidence interval [CI]: 73%–79%) and high risk 79% (95% CI: 66%–87%).

Multiple factors were assessed for prognostic potential, and only ALC was found to be significant ($p = .02$, with wide CIs) (Table 1), although trends were observed (Figure 3). The 2-year OS for patients who received radiotherapy was 100%, in contrast with 89% in those who did not receive this treatment modality ($p = .04$, 95% CI: 80%–

94%). The 2-year PFS was 93% in those who received radiotherapy and 79% in those who did not ($p = .55$, 95% CI: 67%–87%).

4 | DISCUSSION

In this prospective multicentre study, the 93% 2-year OS of paediatric patients with HL in South Africa is higher than the previous 87% 2-year OS reported in our earlier retrospective study, which had a 5-year OS of 79%.⁵ This improvement may be ascribed to the use of a standardised protocol tailored to the local setting, with increased attention paid to supportive care. Most notably, the 2-year OS of patients with HIV and HL has dramatically risen from 65% in 2010¹⁴ to 89%, nearly matching that of the HIV-negative patients. However, the 5-year OS of these patients in the retrospective cohort decreased to 44% due to ongoing opportunistic infections, and this cohort may also experience similar events.

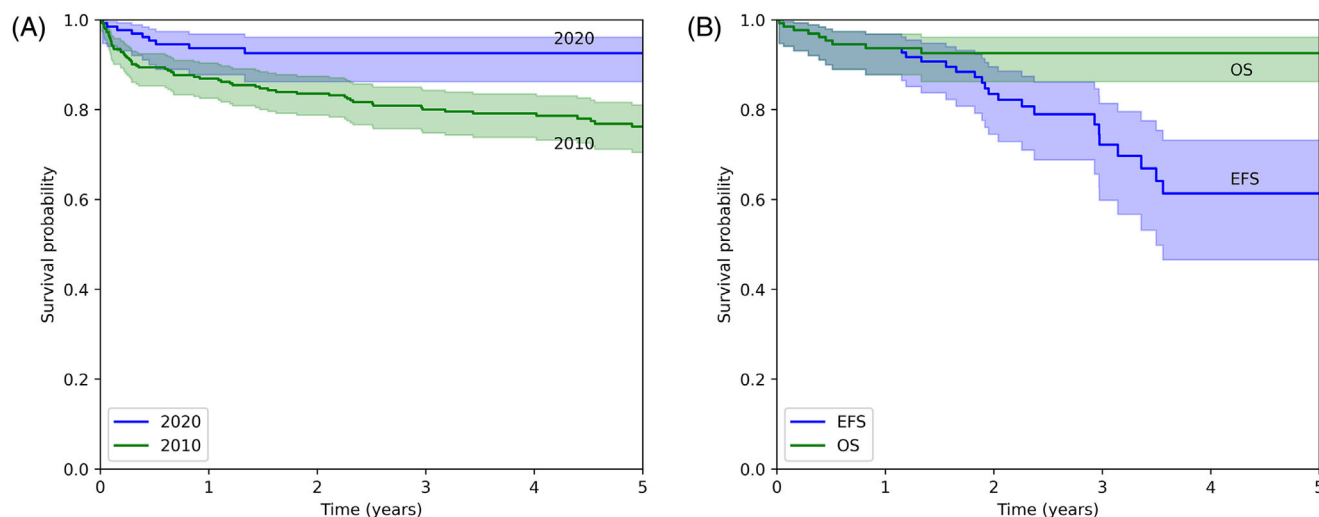


FIGURE 3 Kaplan–Meier survival curves for (A) absolute lymphocyte count (ALC), (B) materna.

The improved 2-year OS is more likely due to improved management of the treatment toxicity with better supportive care than choice of chemotherapy regimen. The analysis of the retrospective cohort, however, did reveal that treatment with ABVD rather than ABVD–ChlVPP or OEPA/OPPA–COPP was associated with less toxicity.⁵

The percentage of patients with HIV in this study (14%) is higher than that of the historical cohort (10%), while the rate of HIV infection in the general paediatric population has decreased over the same period.¹⁵ This may reflect the phenomenon of an increasing incidence of HL in patients with HIV who survive longer nowadays, having evaded mortality from HIV-related opportunistic infections.

The improved 2-year OS and PFS may partially be ascribed to standardised treatment and increased supportive care, but may also reflect improved access to the healthcare system and changing demographic patterns. In contrast to our earlier study, HIV infection is no longer an adverse prognosticator, possibly reflecting increased competence in treating children with both HIV and HL or again reflecting the benefits of being treated according to standardised guidelines. It is also possible that decreased stigma and wider access to antiretroviral therapy contributed to this improvement. Children treated on randomised controlled trials are often shown to have good survival rates, although a definitive systematic review found no clear benefit, concluding that insufficient data exist to support this oft-quoted assertion.¹⁶

Although most potential prognostic factors were not shown to be statistically significant (Table 1), differences remain that may become significant with larger patient numbers (Figure 3). Alternatively, these results may suggest that adverse predictors may be largely overcome in patients receiving adequate multimodal therapy using risk stratification and response adaptation. This approach, more tailored to the individual patient, is relatively simple to implement⁹ and achieves the goal of reserving radiotherapy for patients with SER disease, thus decreasing the number of patients at risk for radiotherapy-related late effects. The CHIPS score, shown to be predictive in intermediate-risk patients treated on doxorubicin hydrochloride, bleomycin, vincristine, etoposide, prednisone and cyclophosphamide (ABVE-PC),¹³ was per-

haps not predictive here, because the score does not accurately prognosticate in this population treated on a different regimen.

The rate of abandonment is relatively low, which we attribute to the means-based partial or complete subsidisation of medical care, as well as additional support from various non-governmental organisations. Despite abandoning therapy, these patients were documented to be alive, perhaps suggesting that decreased treatment intensity might be appropriate, but it must be noted that the period of follow-up is as yet too short to confirm this, and some patients may yet relapse. Nevertheless, further efforts should continue to address treatment abandonment.

Treatment-related mortality represented two-thirds of the deaths in contrast with 33% in the historical cohort, although again, the numbers in the current study are too low to make meaningful comparisons and the study is ongoing. Newly established POU with fewer resources participated in this study, and increasing experience with the protocol may result in decreasing toxicity.

The rate of treatment failure is in keeping with studies in well-resourced settings¹⁷ and lower than in a similar setting in Iran,¹⁸ although the latter study did not have histological confirmation, and refractory disease was diagnosed based on end-of-treatment PET-CT. Numerous studies have failed to show survival benefit with end-of-treatment (EOT) PET-CT in lymphoma.¹⁹ The incidence of relapsed disease will require more time on study and the accrual of more patients over time to indicate whether these results will hold.

According to the study protocol, radiotherapy was indicated in 46% of patients, but only 56% of these received this treatment, and there was a significant difference in 2-year OS but not PFS between patients who did and did not receive radiotherapy. The role of radiotherapy in HL continues to be explored, and research efforts are ongoing to better define the small group of patients that require this modality for cure. An 80% OS was achieved in a study of patients in Burkina Faso, Cameroon, Mali, Madagascar and Senegal, low-income countries without access to radiotherapy.²⁰

Although seven patients were inappropriately treated on the intermediate-risk rather than the high-risk arm, the OS is still high. As South African clinician-researchers continue to gain experience in protocol-based harmonised treatment and clinical trials, we anticipate that adherence to protocols will improve. This relatively large patient cohort observed prospectively, adds valuable insights into the treatment of children and adolescents with HL, and is generalisable to a middle-income setting as there were no exclusions based on HIV status or prior comorbidities, a common factor in clinical trials.

Although this study protocol encouraged bone marrow biopsy for all patients, it is no longer required in settings that have PET-CT facilities available.²¹ Unfortunately, most African countries do not have access to this diagnostic modality and thus should continue to perform bone marrow biopsies, especially in patients with suspected late-stage disease.

This collaborative effort using a risk-stratified and response-adjusted treatment regimen that incorporated agents with a favourable toxicity profile, which are readily available in the local setting and which can be administered on an outpatient basis, resulted in improved survival of children with HL in South Africa.

4.1 | Limitations

Although we enrolled the majority of children with HL in South Africa during the study period, the numbers are small, and robust conclusions are yet to be derived. The proportion of patients with unspecified histological subtypes reflects suboptimal access to paediatric surgery for lymph node excision, as well as a certain number of patients who were too ill at diagnosis to undergo invasive procedures. Overdiagnosis of relapsed or refractory disease should be mitigated by a forthcoming national protocol to diagnose and treat such disease in South Africa. Relapse rates may increase as patients spend more time on the study. Failure to adhere to the protocol and inconsistent access to PET-CT facilities represent challenges in the middle-income setting.

4.2 | Recommendations

Following the success of a harmonised treatment guideline for HL, guidelines for the remaining WHO index cancers should be completed and implemented in South Africa. Multiple studies have now demonstrated the success of ATRs in LMIC, and we thus encourage other countries and cooperative groups to craft ATRs tailored to their individual settings while still following accepted guidelines. In addition, analysing and disseminating results of ATR implementation to accrue sufficient patient numbers for conclusive results are recommended. Children with HIV and HL should receive risk-stratified, response-adapted therapy, with additional supportive care and the option to de-intensify treatment if necessary.

5 | CONCLUSION

In South Africa, risk stratification for HL appears to correlate with prognosis, although larger numbers are required to confirm this with statistical significance. Response-adapted therapy is feasible, although challenging, in South Africa and contributes to a patient-centred approach. The 2-year OS of both HIV-positive and HIV-negative patients has improved dramatically since 2010, most likely due to standardisation of supportive care. This analysis suggests improved OS over time, partially ascribed to standardised treatment and increased supportive care. The improved survival lends strength to the harmonisation movement and gives hope that South Africa will achieve the GICC goals.

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CONFLICT OF INTEREST STATEMENT

The authors declare they have no conflicts of interest.

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DATA AVAILABILITY STATEMENT

The dataset for this study is available on request.

ORCID

Jennifer Geel  <https://orcid.org/0000-0001-8792-3251>

Anel van Zyl  <https://orcid.org/0000-0003-3370-0874>

Jan du Plessis  <https://orcid.org/0000-0002-1914-4202>

Marc Hendricks  <https://orcid.org/0000-0002-3636-0994>

Yasmin Goga  <https://orcid.org/0000-0002-6740-2376>

Amy Carr  <https://orcid.org/0009-0004-2215-2264>

Beverley Neethling  <https://orcid.org/0000-0002-7580-8042>

Artsiom Hramyka  <https://orcid.org/0000-0001-8693-8320>

Fareed Omar  <https://orcid.org/0000-0002-2319-1087>

Rema Mathew  <https://orcid.org/0000-0002-9390-269X>

Lizette Louw  <https://orcid.org/0000-0002-4146-2485>

Thandeka Ngcana  <https://orcid.org/0000-0003-4802-6317>

Tanya Schickerling  <https://orcid.org/0000-0002-6091-204X>

Vutshilo Netshituni  <https://orcid.org/0000-0003-2169-6038>

Liez du Plessis  <https://orcid.org/0000-0002-6321-2751>

Tom Kelsey  <https://orcid.org/0000-0002-8091-1458>

Daynia E. Ballot  <https://orcid.org/0000-0003-4985-048X>
 Monika L. Metzger  <https://orcid.org/0000-0002-7102-4611>

REFERENCES

- Mechita NB, Cherkaoui S, Abousselmam L, et al. Implementing the WHO Global Initiative for Childhood Cancer in Morocco: survival study for the six indexed childhood cancers. *Pediatr Blood Cancer*. 2022;69(10):e29788. doi:10.1002/pbc.29788
- Soliman RM, Elhaddad A, Oke J, et al. Temporal trends in childhood cancer survival in Egypt, 2007 to 2017: a large retrospective study of 14 808 children with cancer from the Children's Cancer Hospital Egypt. *Int J Cancer*. 2020;148:1562-1574. doi:10.1002/ijc.33321
- Mauz-Körholz C, Metzger ML, Kelly KM, et al. Pediatric Hodgkin lymphoma. *J Clin Oncol*. 2015;33(27):2975-2985. doi:10.1200/JCO.2014.59.4853
- World Health Organization. CureAll Framework: WHO global initiative for childhood cancer: increasing access, advancing quality, saving lives. World Health Organization; 2021. Accessed August 12, 2022. <https://apps.who.int/iris/handle/10665/347370>
- Geel JA, Chirwa TC, Rowe B, et al. Treatment outcomes of children with Hodgkin lymphoma between 2000 and 2010: first report by the South African Children's Cancer Study Group. *Pediatr Blood Cancer*. 2017;64(10):e26536. doi:10.1002/pbc.26536
- Beringer N, Bennett KG, Poole JE, Geel JA. Determinants of survival in children with cancer in Johannesburg, South Africa. *S Afr J Oncol*. 2021;5:a189. doi:10.4102/sajo.v5i0.189
- Stones DK, De Bruin GP, Esterhuizen T, Stefan DC. Childhood cancer survival rates in two South African units. *S Afr Med J*. 2014;104(7):502-504.
- Uniform Patient Fee Schedule—National Department of Health. National Department of Health. Accessed February 2, 2023. <https://www.health.gov.za/uniform-patient-fee-schedule/>
- Geel J, Hendricks M, Goga Y, et al. SACCSG HL-2018. Barriers and enablers of a harmonized treatment protocol for childhood and adolescent Hodgkin lymphoma in South Africa. *Pediatr Hematol Oncol*. 2023;40(03):300-313. doi:10.1080/08880018.2022.2162651
- Cheson BD. Staging and response assessment in lymphomas: the new Lugano classification. *Chin Clin Oncol*. 2015;4(1):5. doi:10.3978/j.issn.2304-3865.2014.11.03
- Meignan M, Gallamini A, Haioun C. Report on the first international workshop on interim-PET scan in lymphoma. *Leuk Lymphoma*. 2009;50(8):1257-1260. doi:10.1080/10428190903040048
- Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: building an international community of software platform partners. *J Biomed Inform*. 2019;95:103208. doi:10.1016/j.jbi.2019.103208
- Schwartz CL, Constine LS, Kelly KM, et al. Childhood Hodgkin International Prognostic Score (CHIPS) predicts event-free survival in Hodgkin lymphoma: a report from the Children's Oncology Group. *Pediatr Blood Cancer*. 2017;64(4):e26278. doi:10.1002/pbc.26278
- Geel JA, Eyal KC, Hendricks MG, et al. Prognostic factors affecting survival in children and adolescents with HIV and Hodgkin lymphoma in South Africa. *Leuk Lymphoma*. 2020;62(12):2854-2863. doi:10.1080/10428194.2020.1852472
- Children (0–14) living with HIV—South Africa | Data. World Bank. Accessed February 11, 2023. <https://data.worldbank.org/indicator/SH.HIV.0014?locations=ZA>
- Peppercorn JM, Weeks JC, Cook EF, Joffe S. Comparison of outcomes in cancer patients treated within and outside clinical trials: conceptual framework and structured review. *Lancet North Am Ed*. 2004;363(9405):263-270. doi:10.1016/S0140-6736(03)15383-4
- Daw S, Wynn R, Wallace H. Management of relapsed and refractory classical Hodgkin lymphoma in children and adolescents: review. *Br J Haematol*. 2011;152(3):249-260. doi:10.1111/j.1365-2141.2010.08455.x
- Mehrvar A, Tashvighi M, Nourian M, et al. Childhood Hodgkin lymphoma in Iran; survival and outcome. *Pediatr Hematol Oncol J*. 2020;5(3):100-105. doi:10.1016/j.phoj.2020.06.008
- Adams HJA, Kwee TC. Systematic review on the value of end-of-treatment FDG-PET in improving overall survival of lymphoma patients. *Ann Hematol*. 2020;99(1):1-5. doi:10.1007/s00277-019-03881-x
- Diagne Akonde FB, Togo B, Moreira C, et al. Treatment of childhood Hodgkin lymphoma in sub-Saharan Africa: a report from the French-African Paediatric Oncology Group (GFAOP). *S Afr J Child Health*. 2020;14(3):155-160. doi:10.7196/SAJCH.2020.v14i3.01723
- Hines-Thomas MR, Howard SC, Hudson MM, et al. Utility of bone marrow biopsy at diagnosis in pediatric Hodgkin's lymphoma. *Haematologica*. 2010;95(10):1691-1696. doi:10.3324/haematol.2010.025072

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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Chapter 6. Changes in blood tests correlate with PET-CT results

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Machine Learning to Predict Interim Response in Pediatric Classical Hodgkin Lymphoma Using Affordable Blood Tests

Jennifer A. Geel, MBChB, MMed¹ ; Ansim Hramyka, PhD² ; Jan du Plessis, MBChB, MMed, MPhil^{3,4} ; Yasmin Goga, MBBCh, MSc^{5,6} ; Angel Van Zyl, MBChB, MMed, PhD⁷ ; Marc G. Hendricks, MBChB, PhD^{8,9} ; Thirunushree Naidoo, MBChB¹⁰ ; Rema Mathew, MBChB, MSc^{11,12} ; Lizette Louw, MBChB¹³ ; Amy Carr, MBChB^{5,6} ; Beverley Neethling, MBChB^{5,14} ; Tanya M. Schickerling, MBChB, MMed¹⁵ ; Fareed Omar, MBChB, MMed¹⁶ ; Liezl Du Plessis, MBChB, MMed¹⁷ ; Elelwani Madzhia, MBChB, MMed^{18,19} ; Vhutshilo Netshituni, MBChB^{20,21} ; Katherine Eyal, MCom, PhD, BSc, BCom(Hons)^{9,22} ; Thandeka V.Z. Ngcana, MBChB, MMed²³ ; Tom Kelsey, PhD, MSc, BSc² ; Daynia E. Ballot, MBBCh, PhD²⁴ and Monika L. Metzger, MD, PhD²⁵ for the South African Children's Cancer Study Group

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ABSTRACT

PURPOSE Response assessment of classical Hodgkin lymphoma (cHL) with positron emission tomography-computerized tomography (PET-CT) is standard of care in well-resourced settings but unavailable in most African countries. We aimed to investigate correlations between changes in PET-CT findings at interim analysis with changes in blood test results in pediatric patients with cHL in 17 South African centers.

METHODS Changes in ferritin, lactate dehydrogenase (LDH), erythrocyte sedimentation rate (ESR), albumin, total white cell count (TWC), absolute lymphocyte count (ALC), and absolute eosinophil count were compared with PET-CT Deauville scores (DS) after two cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine in 84 pediatric patients with cHL. DS 1–3 denoted rapid early response (RER) while DS 4–5 denoted slow early response (SER). Missing values were imputed using the k-nearest neighbor algorithm. Baseline and follow-up blood test values were combined into a single difference variable. Data were split into training and testing sets for analysis using Python scikit-learn 1.2.2 with logistic regression, random forests, naïve Bayes, and support vector machine classifiers.

RESULTS Random forest analysis achieved the best validated test accuracy of 73% when predicting RER or SER from blood samples. When applied to the full data set, the optimal model had a predictive accuracy of 80% and a receiver operating characteristic AUC of 89%. The most predictive variable was the differences in ALC, contributing 21% to the model. Differences in ferritin, LDH, and TWC contributed 15%–16%. Differences in ESR, hemoglobin, and albumin contributed 11%–12%.

CONCLUSION Changes in low-cost, widely available blood tests may predict chemosensitivity for pediatric cHL without access to PET-CT, identifying patients who may not require radiotherapy. Changes in these nonspecific blood tests should be assessed in combination with clinical findings and available imaging to avoid undertreatment.

ACCOMPANYING CONTENT

- Appendix
- Data Supplement
- Protocol

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INTRODUCTION

Pediatric Hodgkin lymphoma, a focus cancer in the WHO Global Initiative for Childhood Cancer, is highly curable with traditional chemotherapy.¹ Response-adapted management of classical Hodgkin lymphoma (cHL) using positron emission tomography-computerized tomography (PET-CT) has become the standard approach to determine chemosensitivity by monitoring functional and anatomic treatment

response.^{2,3} Interim PET-CT (iPET-CT) assessment is considered to have excellent negative predictive value (NPV), but suboptimal positive predictive value (PPV), with a resolution of metabolic activity providing reassurance of adequate response, but limited confidence if the iPET-CT shows active disease.⁴ Response evaluation performed after two cycles of chemotherapy is used to identify patients who require treatment intensification with radiotherapy. Although PET-CT facilities are present at most major treatment centers in

CONTEXT

Key Objective

Using machine learning models, we predicted interim positron emission tomography-computerized tomography by using changes in blood test results in pediatric patients with classical Hodgkin lymphoma in 17 South African centers.

Knowledge Generated

The most predictive variable was the difference in absolute lymphocyte count, followed by changes in ferritin, lactate dehydrogenase, and total white cell count. Differences in erythrocyte sedimentation rate, hemoglobin, and albumin contributed less to the model.

Relevance

The findings are not currently applicable in clinical contexts. Once we have accrued more data, we will be able to run simulations to determine whether these findings can be used to direct treatment of individual patients.

South Africa,⁵ there are periods when this imaging is not available. PET-CT facilities are also unavailable in most other African countries and many other low- and middle-income countries (LMICs),⁶ necessitating the search for low-cost alternatives.

The ability to predict which patients will survive (overall survival [OS]) or experience relapse or refractory disease (progression-free survival [PFS]) is well described, using disease-specific parameters such as bulky disease, B symptoms and tumor volume, as well as various individual blood tests.⁷⁻⁹ These include total white cell count (TWC), absolute lymphocyte count (ALC), absolute eosinophil count (AEC), erythrocyte sedimentation rate (ESR), lactate dehydrogenase (LDH), ferritin, copper, and albumin levels.^{7,9-12}

Such parameters have been used to predict OS but not early response to chemotherapy. In South Africa, these blood tests are widely available and the cost of these tests in combination is significantly less than that of a single PET-CT scan. Despite satisfactory sensitivity, the diagnostic utility of these markers is limited by their lack of specificity, and the combination has not been studied in children and adolescents to predict treatment response.

Predictive modeling is an appealing option to aid early identification of patients with suboptimal iPET-CT response. We aimed to assess whether alterations in multiple blood markers, individually and collectively, could forecast rapid early response (RER) or slow early response (SER) on iPET-CT after two cycles of initial doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) therapy through the application of machine learning models.

METHODS

The study was approved by the University of the Witwatersrand Human Research Ethics Committee (M1711100), and the ethics committees of each participating pediatric

oncology unit (POU), and registered on the National Health Research Database and the seven Provincial Health Research Databases in which POU were located. Patients and guardians signed informed assent or consent for inclusion of data in this study.

Seventeen POU prospectively enrolled patients younger than 19 years newly diagnosed with cHL onto a risk-stratified, response-adapted treatment protocol (SACCSG-HL-2018) from July 2016 to July 2022. Patients were staged according to the Ann Arbor staging system and risk-classified. Low-risk disease included stages IA, IB, and IIA; intermediate-risk disease was defined as stages I and II with risk factors (bulky or extranodal disease) and stage IIIA; and high-risk disease included stage II with both bulky disease and extranodal disease, stage III with any risk factors (B symptoms, bulky disease or extranodal disease), and all stage IV disease.¹³

For the majority of patients treated in the state sector, blood tests were performed at National Health Laboratory Services, an integrated network of accredited laboratories.¹⁴ Patients treated in the private sector had blood tests performed at Lancet Laboratories and Ampath Laboratories, which are multiply accredited and considered reference laboratories for various African countries.^{15,16} Blood samples were withdrawn by qualified nurses, phlebotomists, and doctors, and each test was performed once, as standard of care was provided and resources are limited.

Patients with low- and intermediate-risk disease received four and six courses of ABVD, respectively. Patients with high-risk disease received two courses of ABVD, followed by four courses of cyclophosphamide, vincristine, prednisone, and dacarbazine. Those with SER on the basis of persistent metabolic activity and those with bulky mediastinal disease received consolidation radiotherapy.

Data were entered into a secure, online REDCap database¹⁷ at each POU and collated in a central database by the PI who

managed the database and initiated meetings, both online and in person, to facilitate uniformity of data capture and quality control.

Sample size estimation by the Bland-Altman method determined that data sets from 41 patients were required to calculate the receiver operating characteristic (ROC) curves to detect or fail to detect a difference of 3.6% from the reported AUC at 80% power and 5% significance.^{18,19} We analyzed relative changes in hematologic values (TWC, ALC, AEC, and hemoglobin) and nonspecific markers (ferritin, LDH, ESR, albumin, and copper) in comparison with Deauville scores (DS) on iPET-CT assessment after two cycles of ABVD. The first time point was at diagnosis and the second was at early response evaluation, at the start of the third cycle of chemotherapy. RER was classified as DS 1-3, while SER was classified as DS 4-5.²⁰ We included patients who had a PET-CT performed both at baseline and response evaluation. The iPET-CT was performed as close as possible before the third cycle of chemotherapy without delaying the next cycle. Marker values at baseline and response evaluation were reported as mean, median, and range, and differences between clinical characteristics were assessed with the paired *t*-test for normally distributed data or the Wilcoxon signed-rank test for non-parametric data.^{21,22}

We excluded patients with HIV infection as values of ESR, albumin, LDH, ferritin, TLC, AEC, and hemoglobin may differ from those of HIV-negative patients²³ and may not reflect the same PPV for the iPET-CT response.

Abandonment and loss to follow-up were censored in the survival curves. OS was defined as the time from diagnosis to death from any cause. PFS was defined as the time from diagnosis to date of confirmation of relapsed or refractory disease, or death. Patients who did not experience an event were censored at the date of the last follow-up, and data lock was on 30 June 2023.

Data analysis was performed by health data science experts with Python 3.10 and scikit-learn 1.2.2. The baseline and interim blood test values were combined into a single difference variable. Data were split into training and testing sets for analysis with a set of machine learning models (logistic regression, random forests, naïve Bayes, and support vector machine classifiers). Missing values were imputed using a *k*-nearest neighbor (KNN) algorithm. For a given missing feature value in a row, KNN identifies *k* closest rows (neighbors) on the basis of similarity across other available features. These *k* closest rows are then used to determine the value of missing feature using summary statistics, such as mean and median. This provides an estimated value to impute for the missing data point. In our case, we used *k* = 2. We excluded copper from the final model because it had missing values due to unanticipated difficulties performing the test (37% missing at first presentation and 57% missing at interim assessment).

We derived random forest models that (1) predict response to chemotherapy and (2) supply important information into which characteristics contribute most to the response. Random forest is a machine learning algorithm comprising multiple decision trees to aggregate predictions from these trees and select the majority vote to determine the final outcome. Instead of using all available features, random selection is made at each split to reduce overfitting. We tested multiple standard machine learning classifiers and random forest achieved the highest performance on our data set, using methodology similar to Meti et al.²⁴

ROC analysis was performed to assess the utility of baseline markers at diagnosis and at response evaluation for predicting iPET-CT response and to determine the best threshold values. For the ROC-derived AUC, *P* values were calculated to determine the cutoff points for the most accurate response-to-therapy prediction. Sensitivity, specificity, accuracy, PPV, and NPV were calculated using ROC curve threshold values. PPV was defined as the ability to predict SER on iPET-CT. Misclassification rates, calculated from the confusion matrix, express how often the confusion matrix is incorrect in predicting actual positive and negative outputs.

RESULTS

Patient Population

We enrolled 132 consecutive previously untreated patients with histologically proven cHL in the SACCSG HL-2018 study. PET-CT was performed at baseline in 111; of these, 96 had an iPET-CT performed. Twelve patients (13%) with HIV were excluded while 84 (87%) were HIV-negative and were analyzed in this study (Fig 1).

The median age was 9.7 years (range, 2.3-16.9 years; IQR, 6.9-12.7 years), with seven patients (8%) classified as low-risk, 24 (29%) as intermediate-risk, and 53 (63%) as high-risk. Comorbidities included tuberculosis in two patients, vanishing bile duct syndrome (1), idiopathic central precocious puberty (1), noncommunicating hydrocephalus (1), dilated cardiomyopathy (1), vitiligo (1), and decreased cardiac ejection fraction (1). After iPET-CT, 57 patients (68%) demonstrated RER and 27 (32%) demonstrated SER (Table 1).

Hematologic values and nonspecific markers

None of the patients with hypoalbuminemia had nephrotic syndrome. At response evaluation, significant rises in hemoglobin and albumin (*P* < .001) and decreases in TWC, ESR, copper, LDH, and ferritin (all *P* < .001) were noted. Elevations in ALC and AEC were not statistically significant (*P* = .14 and .88, respectively; Fig 2; Data Supplement, Table S1).

After Bayesian optimization of model hyperparameters, random forest analysis achieved a validated test accuracy of

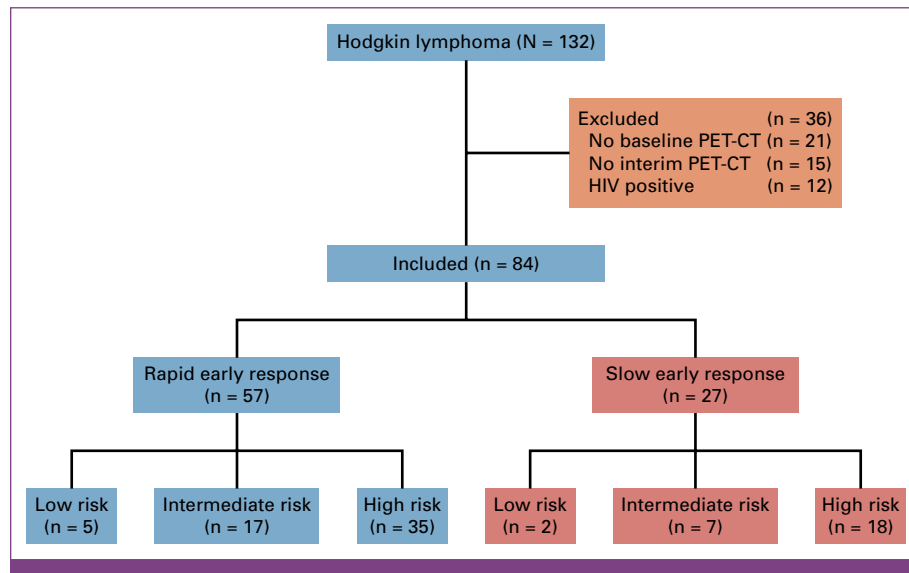


FIG 1. Interim assessment and risk stratification of pediatric patients on SACC SG-HL-2018. PET-CT, positron emission tomography-computerized tomography.

77% when predicting RER or SER from blood samples. The performance of other classifiers was inferior. The optimal model had a predictive accuracy of 86% and an ROC AUC of 93%, with a 95% confidence interval of 87%–98% (Fig 3A).

The sensitivity was 85% and the specificity was 86%, with a misclassification rate of 14% (Fig 3B). The model has a PPV of 74% in determining SER, and an NPV of 93% in predicting RER. Differences in ferritin, LDH, and TWC contributed 16%, 15%, and 14% respectively. Differences in ESR, hemoglobin, and albumin each contributed 11%–12%.

After a median follow-up of 2 years (range, 0.1–7.6 years), the 2-year OS was 95.3% for patients with RER and 96.4% for patients with SER ($P = .72$). PFS was 91.5% for patients with RER and 85.1% for patients with SER ($P = .3$; Fig 4).

DISCUSSION

We show that the combined changes in certain hematologic parameters and nonspecific laboratory markers correlate with chemotherapy response on the basis of iPET-CT after two cycles of ABVD in pediatric patients with cHL. The most significant contributors to the study model were changes in ALC. Following closely were differences in LDH, AEC, and ferritin, which also showed strong predictive capabilities. Changes in TWC, ESR, hemoglobin, and albumin had a slightly lesser impact on the model's predictions. In combination, the changes in these simple blood markers offer more information than singly and can be used to predict response on iPET-CT.

As PET-CT has been shown to have a high number of false-positive FDG-avid lesions, it has more utility in excluding treatment failure and less in identifying treatment

failure.^{25,26} The findings of this study highlight the potential benefits of monitoring changes in these blood tests as a means to predict the response to chemotherapy. Specifically, the observed changes in blood tests demonstrate a notable advantage in predicting RER rather than SER.

Although the changes in these blood tests cannot assist with the assessment of anatomic response, they offer value in assessing functional or metabolic response. In a previous study, an analysis of the individual baseline blood tests did not demonstrate the ability to predict 2-year OS.¹³ The current study does not focus on the prediction of survival but on the prediction of iPET-CT response after two cycles of ABVD.

Chemosensitivity is commonly predicted by iPET-CT performed after two cycles of chemotherapy, including ABVD.²⁷ This response is used to guide further treatment by increasing treatment intensity, consolidating with radiotherapy or decreasing treatment intensity as in the de-escalation of escalated BEACOPP.^{8,25,28} iPET-CT has better PPV for predicting which patients will be long-term survivors but is less accurate at predicting which patients will develop progressive or relapsed disease.²⁵ It thus has limited value in identifying patients who require intensification.

The limitations of nonspecific tumor markers in pediatric cHL highlight the need for more specific and sensitive diagnostic tools. PET-CT also has several limitations, including exposure to radiation, time commitment, and high cost, making it inaccessible in many low- and middle-income settings.⁶ Incorporating changes in sizes of malignant masses using chest x-rays and CT scans in combination with changes in blood tests may prove to be useful in resource-constrained settings.

TABLE 1. Baseline Characteristics of Children and Adolescents With Hodgkin Lymphoma

Parameter	No. (%)
Sex	
Male	21 (25)
Female	63 (75)
Age, years	
Median (IQR)	9.7 (6.9-12.7)
Range	2.3-16.9
BMI	
Obese/overweight	3 (4)
Adequate	63 (75)
<2 standard deviations	18 (21)
Histologic subtype	
Nodular sclerosing	51 (61)
Mixed cellularity	19 (23)
Lymphocyte-rich	2 (2)
Lymphocyte-depleted	1 (1)
HL NOS	11 (13)
Stage	
I	2 (2)
II	29 (35)
III	27 (32)
IV	26 (31)
B symptoms	
Yes	52 (62)
No	32 (38)
Bulky disease	
Yes	52 (62)
No	32 (38)
Autoimmune manifestations of HL	
Yes	7 (8)
No	77 (92)
Risk group	
Low risk	7 (8)
Intermediate risk	24 (29)
High risk	53 (63)
Response	
Rapid early response	57 (68)
Slow early response	27 (32)

Abbreviations: HL, Hodgkin lymphoma; NOS, not otherwise specified.

There is thus a need to identify alternative methods that provide similar or better response assessment capabilities. By identifying biomarkers, clinicians could effectively monitor the progress of the disease and adjust the treatment regimen accordingly, leading to improved outcomes. Such markers must be at least as specific and sensitive as FDG-PET-CT imaging which, in itself, is insufficiently specific.

The ideal biomarker would have high PPV and NPV, be cost-effective, minimally invasive, readily available, sensitive and

specific to changes in disease status with high PPV and NPV, and have a short turnaround time to facilitate decision making.²⁹ Thymus and activation-regulated chemokine (TARC) is a promising biomarker that is easily measurable, sensitive, and specific for the disease, and may have a higher PPV than iPET-CT for progressive disease.^{30,31} The platform to set up a TARC testing system is less expensive than setting up a nuclear medicine facility, and an additional blood test is less invasive and inconvenient for patients.²⁹ Other potential serum biomarkers are microRNAs associated with tumor-secreted extracellular vesicles in the circulation of patients with cHL.³² The combination of microRNA with TARC measurements has an AUC of 93%, 93.5% sensitivity, 85% specificity, and an NPV of 96%, but these tests are generally available only in the research setting, and certainly not in LMIC.

Most countries in Africa do not have access to PET-CT and, in those settings where PET-CT machines are available, access may still be limited because of the overwhelming patient numbers, cost, and transport limitations.⁶ Access to traditional chemotherapy is still limited in many countries.^{33,34} Salvage options such as autologous stem-cell transplant and novel targeted agents such as drug-conjugated antibodies and immune checkpoint inhibitors are out of reach for the majority.³⁵ Nevertheless, relatively high survival rates have been achieved with conventional chemotherapy and radiotherapy in many countries using a strategic approach^{34,36} and the results of this study may contribute to improving response-adapted treatment in similar resource-constrained settings.

The ability to predict RER is clinically significant, enabling health care professionals to make informed decisions about treatment plans and allowing for timely adjustments if necessary. The choice to avoid radiotherapy has long-term consequences, decreasing the chances of the development of subsequent malignant neoplasms and other late effects of radiotherapy.³ Conversely, patients who demonstrate SER may require alternative treatment strategies or modifications to their current regimen. By identifying SER timeously, health care providers can proactively address the situation, potentially avoiding delays in achieving the desired therapeutic outcome.

In this study, we used advanced machine learning techniques applied to baseline and interim data to derive a reliable method for discrimination between later RER and SER. A range of classification models, each having strong previous evidence of utility and performance, were fine-tuned using Bayesian optimization to identify the model setting that gave the best validated model performance. The model with the best performance was random forests, a nonparametric stochastic ensemble method that aggregates the results of many individual decision tree models to both guard against overfitting the supplied data and return a model with low predicted error when applied to new and/or unseen cases. The random forest approach method also allows the identification of the most important

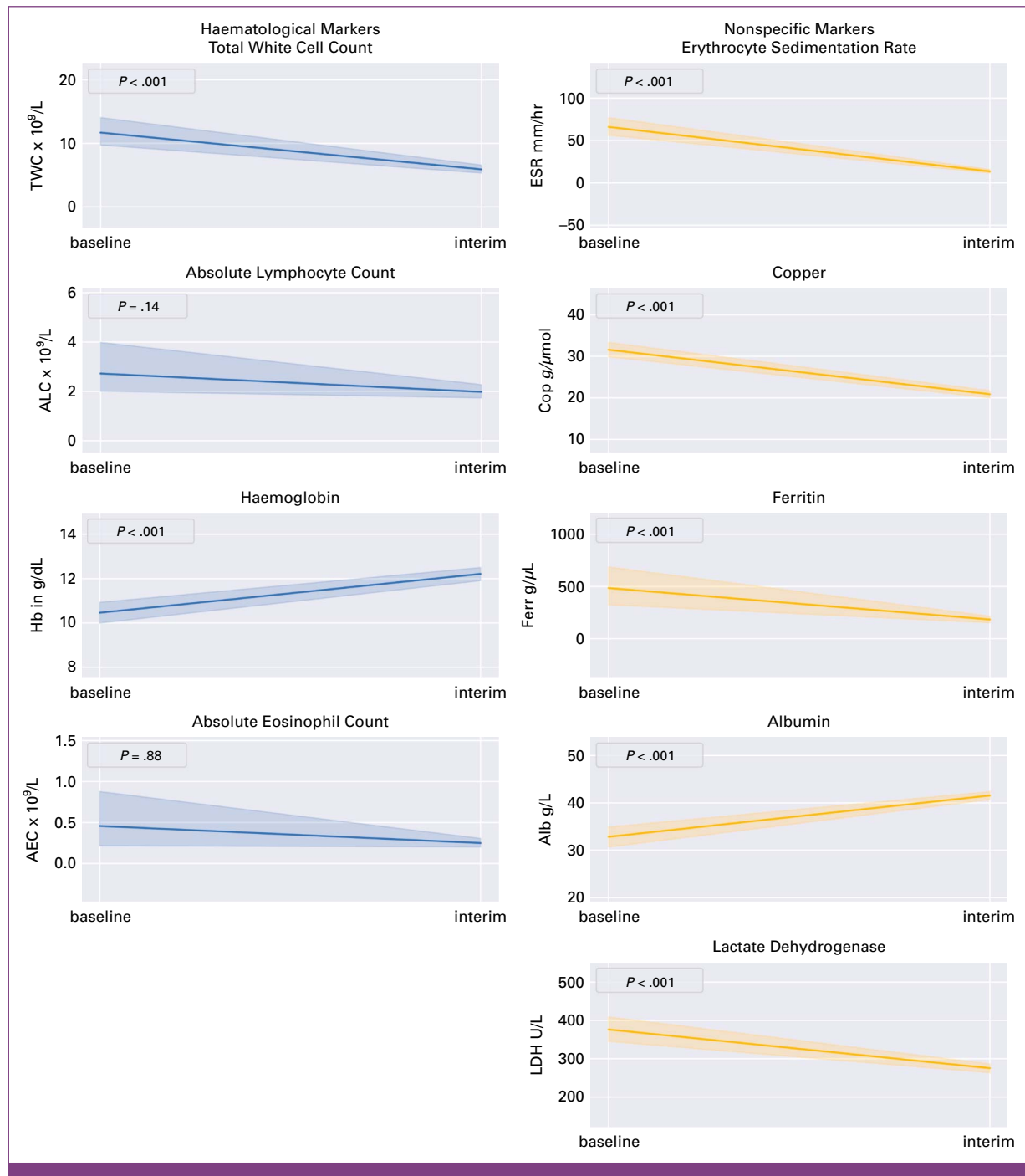


FIG 2. Hematologic parameters and nonspecific markers of pediatric patients on SACC SG-HL-2018 at baseline and interim analysis: (A) TWC, (B) ALC, (C) hemoglobin, (D) AEC, (E) ESR, (F) copper, (G) ferritin, (H) albumin, and (I) LDH. AEC, absolute eosinophil count; ALC, absolute lymphocyte count; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase; TWC, total white cell count.

factors that underpin a prediction of later RER or SER. We show that differences in ESR, ferritin, and albumin are less important for this study, suggesting that future studies should prioritize differences in hemoglobin, ALC, LDH, AEC, and TWC.

More recently, an important goal has been to predict the subset of patients who will relapse to intensify treatment for

these patients.²⁹ iPET-CT alone is insufficient for this purpose, but the combination of blood tests and iPET-CT results may in time yield further useful information. The potential correlation between iPET-CT and patient survival is as yet inconclusive in our patient cohort, as demonstrated by the similar 2-year OS in patients with RER and SER. We may postulate that by escalating treatment guided by iPET-CT, the survival disparity has effectively been reduced. The

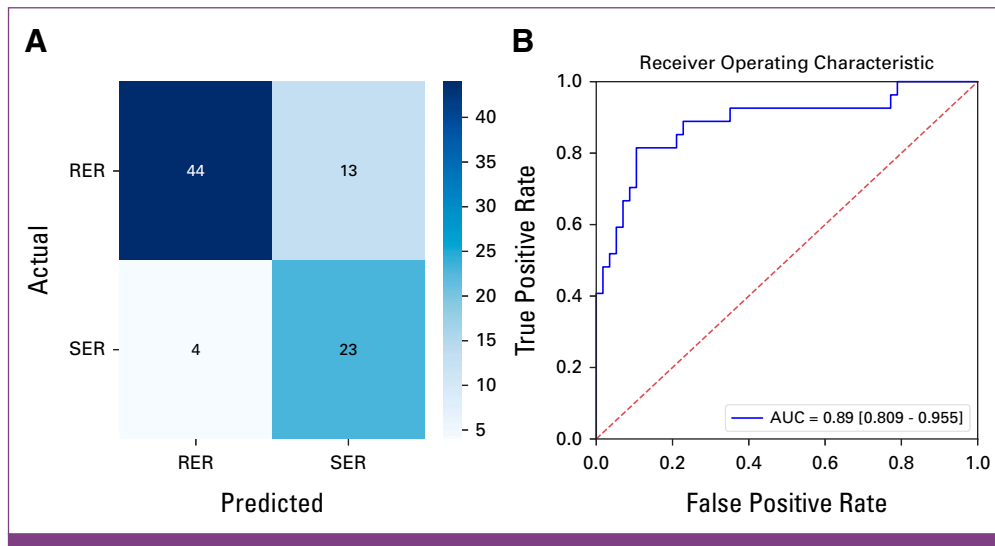


FIG 3. Prediction of chemosensitivity of pediatric patients with classical Hodgkin lymphoma. (A) Receiver operating characteristic curve. (B) Confusion matrix. RER, rapid early response; SER, slow early response.

quest to predict relapse or progression continues, especially in settings where salvage options are limited.

Although the results of this study are useful in predicting iPET-CT response, the challenge remains to tailor treatment safely and appropriately, to effect cure with minimal side effects, and to identify those patients who require treatment intensification with accuracy. These findings highlight the importance of monitoring changes in blood tests as they offer valuable insights into the prediction of RER to chemotherapy. By leveraging these predictive markers, health care professionals in resource-limited settings may be able

to optimize treatment plans, personalize care, and enhance patient outcomes. However, caution should be exercised in settings with potentially diverse patient populations: different patient groups may exhibit variations in baseline hematologic parameters or levels of nonspecific markers. These variations may be influenced by a range of factors, including underlying medical conditions, demographic characteristics, and environmental factors.

Challenges now include the translation of these results into a format with clinical utility. The envisaged solution is the development of a practical scoring system or a mobile smartphone application. Such tools would allow for the input of blood test results to generate a score indicating whether radiotherapy can be safely avoided. In settings where radiation therapy is not available, such tools may not be as relevant, but may still be of value to predict survival. Ultimately, the goal is to tailor the treatment regimen for each patient to achieve maximal efficacy with minimal side effects while accurately identifying patients who require treatment intensification.

The study required a minimum of 41 complete patient data sets to ensure precise evaluation through ROC curves. Because of the unavailability of complete data sets, imputation techniques were used. The limitation associated with imputing missing values is anticipated to be addressed to some extent by using 84 data sets, double the required sample size calculation. The final random forest model selected would benefit from more baseline, interim, and outcome data, and hence the results reported in this study are indicative of future model performance rather than definitive. The scope of this investigation solely encompassed analysis of the potential of changes in blood tests to predict iPET-CT response, without considering the subsequent relapse status of

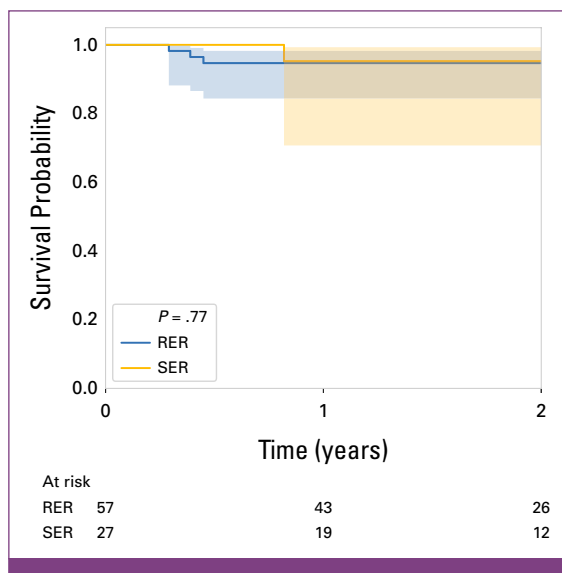


FIG 4. Kaplan-Meier curve of progression-free survival comparing patients with RER and SER. RER, rapid early response; SER, slow early response.

these patients. We did not include risk classification at presentation in the machine learning models as the sample size was too small to provide suitable power.

In conclusion, the pooled changes in certain hematologic parameters and nonspecific laboratory markers exhibit a strong correlation with chemosensitivity, as evaluated through iPET-CT scans after two cycles of ABVD treatment in pediatric patients with cHL. We predicted RER or SER from blood samples with a high level of accuracy. In resource-constrained environments with limited access to PET-CT, these findings offer potential tools to predict chemosensitivity. In such settings, these changes could serve as

substitutes for iPET-CT and thus assist with the identification of pediatric patients with cHL who can safely forgo radiotherapy and avoid its subsequent late effects. These results are not definitive in isolation and should be interpreted in conjunction with other diagnostic tests and clinical findings to establish chemosensitivity accurately. Although these hematologic and nonspecific tumor markers provide valuable insights into disease progression and treatment response, their lower specificity imposes limitations. Consequently, additional research efforts are warranted to identify more specific response-assessment tools for pediatric cHL to give patients in LMIC the best possible chance of cure with high quality of life.

AFFILIATIONS

¹Department of Paediatrics and Child Health, Paediatric Haematology-Oncology, Charlotte Maxeke Johannesburg Academic Hospital, Wits Donald Gordon Medical Centre, University of the Witwatersrand, Johannesburg, South Africa

²Computer Science, St Andrew's University, St Andrew's, United Kingdom

³Universitas Hospital, Bloemfontein, South Africa

⁴Paediatric Haematology-Oncology, University of the Free State, Bloemfontein, South Africa

⁵Paediatric Haematology-Oncology, University of KwaZulu-Natal, Durban, South Africa

⁶Greys Hospital, Pietermaritzburg, South Africa

⁷Faculty of Medicine and Health Sciences, Stellenbosch University and Tygerberg Hospital, Cape Town, South Africa

⁸Red Cross War Memorial Children's Hospital, Cape Town, South Africa

⁹University of Cape Town, Cape Town, South Africa

¹⁰Department of Radiation Sciences, Paediatric Radiation Oncology, Charlotte Maxeke Johannesburg Academic Hospital, Wits Donald Gordon Medical Centre, University of the Witwatersrand, Johannesburg, South Africa

¹¹Frere Hospital, East London, South Africa

¹²Paediatric Haematology-Oncology, Walter Sisulu University, East London, South Africa

¹³Nuclear Medicine, Center of Molecular Imaging and Theranostics, Johannesburg, South Africa

¹⁴Inkosi Albert Luthuli Central Hospital, Durban, South Africa

¹⁵Netcare Alberton Hospital, Alberton, South Africa

¹⁶Paediatric Haematology-Oncology, Steve Biko Academic Hospital, University of Pretoria, Pretoria, South Africa

¹⁷Paediatric Haematology-Oncology, Robert Mangaliso Sobukwe Hospital, Kimberley, South Africa

¹⁸Dr George Mukhari Hospital, Garankuwa, South Africa

¹⁹Paediatric Haematology-Oncology, Sefako Makgatho University, Garankuwa, South Africa

²⁰Polokwane-Mankweng Hospital Complex, Polokwane, South Africa

²¹Paediatric Haematology-Oncology, University of Limpopo, Polokwane, South Africa

²²Southern Africa Labour and Development Research Unit, School of Economics, Cape Town, South Africa

²³Paediatric Haematology-Oncology, Chris Hani Baragwanath Academic Hospital, Wits Donald Gordon Medical Centre, University of the Witwatersrand, Johannesburg, South Africa

²⁴School of Clinical Medicine, University of the Witwatersrand, Johannesburg, South Africa

²⁵Pediatric, Médecins Sans Frontières, Geneva, Switzerland

CORRESPONDING AUTHOR

Tom Kelsey, PhD, MSc, BSc; e-mail: twk@st-andrews.ac.uk.

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DATA SHARING STATEMENT

The dataset for this study is available on request.

AUTHOR CONTRIBUTIONS

Conception and design: Jennifer A. Geel, Artsiom Hramyka, Jan du Plessis, Marc G. Hendricks, Thanushree Naidoo, Rema Mathew, Lizette Louw, Beverley Neethling, Fareed Omar, Elelwani Madzhia, Tom Kelsey, Daynia E. Ballott, Monika L. Metzger

Provision of study materials or patients: Jennifer A. Geel, Yasmin Goga, Anel Van Zyl, Marc G. Hendricks, Thanushree Naidoo, Rema Mathew, Amy Carr, Beverley Neethling, Tanya M. Schickerling, Fareed Omar, Liezl du Plessis, Elelwani Madzhia, Vhutshilo Netshituni, Thandeka V.Z. Ngcana

Collection and assembly of data: Jennifer A. Geel, Jan du Plessis, Yasmin Goga, Anel Van Zyl, Marc G. Hendricks, Rema Mathew, Lizette Louw, Amy Carr, Beverley Neethling, Tanya M. Schickerling, Fareed Omar, Liezl du Plessis, Elelwani Madzhia, Vhutshilo Netshituni, Thandeka V.Z. Ngcana

Data analysis and interpretation: Jennifer A. Geel, Artsiom Hramyka, Katherine Eyal, Tom Kelsey, Monika L. Metzger

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Anel Van Zyl

Consulting or Advisory Role: Roche, Novo Nordisk

Beverley Neethling

Travel, Accommodations, Expenses: SANBS

Monika L. Metzger

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REFERENCES

- World Health Organization: CureAll framework: WHO global initiative for childhood cancer: Increasing access, advancing quality, saving lives. World Health Organization, 2021. <https://apps.who.int/iris/handle/10665/347370>
- Schwartz CL, Constine LS, Villaluna D, et al: A risk-adapted, response-based approach using ABVE-PC for children and adolescents with intermediate- and high-risk Hodgkin lymphoma: The results of P9425. *Blood* 114:2051-2059, 2009
- Mauz-Körholz C, Metzger ML, Kelly KM, et al: Pediatric Hodgkin lymphoma. *J Clin Oncol* 33:2975-2985, 2015
- Ferrari C, Niccoli Asabella A, Merenda N, et al: Pediatric Hodgkin lymphoma predictive value of interim 18 F-FDG PET/CT in therapy response assessment. *Medicine* 96:e5973, 2017
- Vorster M, Doruyter A, Brink A, et al: Recommendations: Appropriate indications for positron emission tomography/computed tomography, 2015. *South Afr Med J* 106:105-122, 2015
- Gallach M, Mikhail Lette M, Abdel-Wahab M, et al: Addressing global inequities in positron emission tomography-computed tomography (PET-CT) for cancer management: A statistical model to guide strategic planning. *Med Sci Monit* 26:e926544, 2020
- Farruggia P, Puccio G, Sala A, et al: The prognostic value of biological markers in paediatric Hodgkin lymphoma. *Eur J Cancer* 52:33-40, 2016
- Jain S, Kapoor G, Bajpai R: ABVD-based therapy for Hodgkin lymphoma in children and adolescents: Lessons learnt in a tertiary care oncology center in a developing country. *Pediatr Blood Cancer* 63:1024-1030, 2016
- Vaughan Hudson B, Linch DC, Macintyre EA, et al: Selective peripheral blood eosinophilia associated with survival advantage in Hodgkin's disease (BNLI report no 31). *British National Lymphoma Investigation. J Clin Pathol* 40:247-250, 1987
- Gözdaşoğlu S, Çavdar AO, Arcasoy A, et al: Serum copper and zinc levels and copper/zinc ratio in pediatric non-Hodgkin's lymphoma. *Acta Haematol* 67:67-70, 1982
- Gupta SK, Shukla VK, Gupta V, et al: Serum trace elements and Cu/Zn ratio in malignant lymphomas in children. *J Trop Pediatr* 40:185-187, 1994
- Hasenclever D, Diehl V: A prognostic score for advanced Hodgkin's disease. International Prognostic Factors Project on Advanced Hodgkin's Disease. *N Engl J Med* 339:1506-1514, 1998
- Geel J, Van Zyl A, Plessis JD, et al: Improved survival of children and adolescents with classical Hodgkin lymphoma treated on a harmonised protocol in South Africa. *Pediatr Blood Cancer* 71:e30712, 2024
- nhlsadmin: Type of tests. National Health Laboratory Service. <https://www.nhls.ac.za/diagnostic-services/type-of-tests/>
- Lancet Laboratory—Welcome to Lancet. <https://www.lancet.co.za/>
- Ampath—Doctors services. <https://www.ampath.co.za/our-services>
- Harris PA, Taylor R, Minor BL, et al: The REDCap consortium: Building an international community of software platform partners. *J Biomed Inform* 95:103208, 2019
- Bland JM, Altman DG: Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1:307-310, 1986
- Bready AP, Longstaff ID: Sample size estimation using the receiver operating characteristic curve. *IEEE 17th International Conference Pattern Recognition (ICPR '04)*, Cambridge, UK, August 26, 2004
- Meignan M, Gallamini A, Meignan M, et al: Report on the first international workshop on interim-PET scan in lymphoma. *Leuk Lymphoma* 50:1257-1260, 2009
- Gosset WS: The probable error of a mean. *Biometrika* 6:1-25, 1908
- Kruskal WH, Wallis WA: Use of ranks in one-criterion variance analysis. *J Am Stat Assoc* 47:583-621, 1952
- Ositadimma M, Ositadimma M, Bright OE, et al: Effect of HIV infection on some haematological parameters and immunoglobulin levels in HIV patients in Benin City, southern Nigeria. *J HIV Retrovirus* 2, 2016
- Meti N, Saednia K, Lagree A, et al: Machine learning frameworks to predict neoadjuvant chemotherapy response in breast cancer using clinical and pathological features. *JCO Clin Cancer Inform* 10.1200/CCI.20.00078
- Adams HJA, Kwee TC: Systematic review on the value of end-of-treatment FDG-PET in improving overall survival of lymphoma patients. *Ann Hematol* 99:1-5, 2020
- Adams HJA, Nievelstein RAJ, Kwee TC: Prognostic value of interim FDG-PET in Hodgkin lymphoma: Systematic review and meta-analysis. *Br J Haematol* 170:356-366, 2015
- Ilivitzki A, Radan L, Ben-Arush M, et al: Early interim FDG PET/CT prediction of treatment response and prognosis in pediatric Hodgkin disease—Added value of low-dose CT. *Pediatr Radiol* 43:86-92, 2013
- Borchmann P, Goergen H, Kobe C, et al: PET-guided treatment in patients with advanced-stage Hodgkin's lymphoma (HD18): Final results of an open-label, international, randomised phase 3 trial by the German Hodgkin Study Group. *Lancet* 390:2790-2802, 2017
- Husi K, Pinczés LI, Fejes Z, et al: Combined prognostic role of TARC and interim 18F-FDG PET/CT in patients with Hodgkin lymphoma-real world observational study. *Hellenic J Nucl Med* 25:125-131, 2022
- Guidetti A, Mazzocchi A, Miceli R, et al: Early reduction of serum TARC levels may predict for success of ABVD as frontline treatment in patients with Hodgkin lymphoma. *Leuk Res* 62:91-97, 2017
- Jones K, Vari F, Keane C, et al: Serum CD163 and TARC as disease response biomarkers in classical Hodgkin lymphoma. *Clin Cancer Res* 19:731-742, 2013
- Drees EEE, Roemer MGM, Groenewegen NJ, et al: Extracellular vesicle miRNA predict FDG-PET status in patients with classical Hodgkin lymphoma. *J Extracell Vesicles* 10:e12121, 2021
- Ngwa W, Addai BW, Adewole I, et al: Cancer in sub-Saharan Africa: A Lancet Oncology Commission. *Lancet Oncol* 23:e251-e312, 2022
- Kochbati L, Fdhila F, Belaid I, et al: La maladie de Hodgkin de l'enfant dans le Nord Tunisien: étude clinique et thérapeutique. *Cancer/Radiothérapie* 16:627-632, 2012
- Kizub D, Naik S, Abogan AA, et al: Access to and affordability of World Health Organization essential medicines for cancer in sub-Saharan Africa: Examples from Kenya, Rwanda, and Uganda. *Oncologist* 27:958-970, 2022
- El-Badawy S, Aboulmaga S, Abou Gabal A, et al: Risk adapted combined modality treatment in children with Hodgkin's disease: NCI, Cairo. *J Egypt Natl Cancer Inst* 20:99-110, 2008

APPENDIX 1. LIST OF SOUTH AFRICAN CHILDREN'S CANCER STUDY GROUP MEMBERS WITH E-MAILS

David Stones (StonesDK@ufs.ac.za); Ruellyn Cockroft (rcockroft@xtra.co.nz); Alan Davidson (alan.davidson@uct.ac.za); Anabela Andrade (a_andrade@mweb.co.za); Ane Buchner (ane.buchner@up.ac.za); Ann Van Eyssen (ann.vaneyssen@uct.ac.za, annveyssen@tiscali.co.za); Barry van Emmenes (barry.vanemmenes@gmail.com); (bernard.goodwin@wits.ac.za); Bianca Rowe (bianca_r@hotmail.com); Clare Stannard (Clare.Stannard@uct.ac.za); Cristina Stefan (cristinastefan10@gmail.com); David Reynders (David.Reynders@up.ac.za); Diane MacKinnon (dianemacleask@gmail.com); Elmarie Mathews (mathews.elmarie@yahoo.co.uk); Farieda Desai (farieda.desai@gmail.com); Gesami Steytler (gesamisteytler@gmail.com); Gita Naidu (gita.naidu@wits.ac.za); Janet Poole (Janet.Poole@wits.ac.za); Jeanette Parkes (jeanette.parkes@uct.ac.za); Johani Vermeulen (johani.vermeulen@gmail.com); Karin Lecuona (Karin.Lecuona@uct.ac.za); Karla Thomas (karlamthomas@yahoo.com, Karla.Thomas@echealth.gov.za); Kate Bennett (kate_bennett@hotmail.com); Kershinee Reddy (kershinee@yahoo.com); Keshnie Moodley (drkeshnie@gmail.com); Komala Pillay (Komala.Pillay@uct.ac.za); Mariana Kruger (marianakruger@sun.ac.za); Jaques van Heerden (jaquesvanheerden@gmail.com);

Linda Wainwright (sjaspan@iafrica.com); Leila Schoonraad (Leilaschoonraad@gmail.com); Lourens de Jager (ldejager@icon.co.za); Mairi Bassingthwaighte (mairi.bass@gmail.com); Manickavallie Vaithilingum (vaithil@medis.co.za); Nicolene Moonsamy (nicolenemoonsamy@gmail.com); Oloko Wedi (olokowedi@yahoo.com); Palessa Radebe (palessa.radebe@gmail.com); Ronelle Uys (ruys@sun.ac.za); Stelios Poyiadjis (stelios.poyiadjis@wits.ac.za); Rajendra Thejpal (thejpal@ukzn.ac.za); Rosemarie Schwyzer (Rosemarie.Schwyzter@wits.ac.za); Johannes Du Plessis (duPlesJP@ufs.ac.za); Candice Hendricks (candice_hendricks@outlook.com); Pieter Hesselning (pbh@sun.ac.za); Barry Vanemmenes (Barry.Vanemmenes@echealth.gov.za); Miss Judy Schoeman (Judy.schoeman@up.ac.za); Mohamed Adamjee (dradamjee@yahoo.co.za); Milind Chitnis (chitnis.m@gmail.com); Pat Hartley (phartley@uct.ac.za); Wendy Mathiassen (wrrwm@iafrica.com); Alistair Millar (Alistair.millar@uct.ac.za); Sr Colleen Wright (cawr@sun.ac.za); Nadia Beringer (nadia.beringer@gmail.com); Ngoakoana Mahlachana (ngoakoanam@yahoo.com); Thandeka Nkabi (thandekankabi@yahoo.com); Jade Flood (jade@floodgates.co.za); Mampoi Jonas (mmorienyane@yahoo.com); Hamidah Van Staaden (hbvanstaaden@yahoo.com); Thurandrie Naicker (thuran.naicker@uct.ac.za); Pawel Schubert (pawels@sun.ac.za); Bulelwa Masoka (bulelwa.masoka@yahoo.com)

Chapter 7. Integrated discussion and conclusion

This study comprised retrospective and prospective components. We aimed to determine baseline survival and prognostic factors of CAYA with cHL in South Africa; determine the feasibility of implementing a comprehensive harmonised management guideline; document 2-year OS and PFS using this harmonised guideline; and create a model to predict chemosensitivity using simple blood tests.

We analysed data from 294 historical cases and prospectively accrued 165 patients, of whom 132 were analysed for publications. In our retrospective cohort we documented the 5-year OS and found that the statistically significant poor prognostic factors were treatment with regimens other than ABVD, HIV infection and advanced stage of disease. This informed our choice to use ABVD prospectively, offer more supportive therapy to HIV-positive patients and intensify treatment for patients with high-risk disease in the harmonised treatment guideline.

We then successfully implemented management guidelines with a standardised diagnostic, staging and treatment approach. We subsequently analysed 2-year OS and found that the survival of both HIV-positive and –negative patients was higher than in the historical cohort. Finally, we showed that the changes in a combination of affordable and readily available simple blood markers could be used to predict chemosensitivity at interim assessment.

Chapter	Objective	Key Findings	Conclusion
2	To identify prognostic factors at presentation that influence 5-year OS in a historical cohort. Potential prognostic factors include B symptoms, Ann Arbor stage, risk group at diagnosis, nutritional status, socio-economic factors, HIV status and levels of non-specific markers.	5-year OS of 84% in HIV-negative patients and 49% in HIV-positive patients - Poor prognostic factors included HIV infection ($p=0.018$), treatment with regimens other than ABVD ($p=0.028$) and Ann Arbor stage III and IV disease ($p=0.006$)	HIV infection significantly impacted on overall survival. The 5-year OS was lower than that documented in both high-income countries and similar African settings. OEPA/OPPA-COPP was associated with higher treatment-related mortality and ABVD-ChlVPP did not offer any survival benefit in the South African setting.
3	To explore survival rates of CAYA with HIV and cHL in a historical cohort, and to determine prognostic factors.	- Poor prognostic factors included albumin level $<20\text{g/dL}$ and $\text{CD4\%} < 15\%$. - Increased mortality due to post-therapy opportunistic and nosocomial infections.	HIV-infected patients were more likely to present with features of malnutrition and advanced disease, impacting on survival. These patients experienced increased mortality due to post-therapy opportunistic and nosocomial infections, identifying a potentially modifiable factor.
4	To determine the feasibility of the introduction of a single harmonised management protocol for CAYA with Hodgkin lymphoma among participating POUs in South Africa.	- The majority of POUs met the minimum criteria to participate. - Chemotherapy and radiotherapy availability nearly 100% of the time. - Barriers to participation included excessive time to obtain regulatory approvals, time constraints and lack of dedicated research staff.	Multicentre collaboration and harmonisation of management protocols are achievable in a middle-income setting. Minimal funding is required but full participation to run high-quality studies requires more financial investment.

		Enablers included the simple management algorithm and communication tools.	Focused funding and increased prioritisation of research may address systemic barriers to full participation.
5	To describe outcomes of patients treated on a single harmonised protocol and to compare outcomes of these patients with those of a historical cohort in the same setting. These outcomes include two-year survival rates (progression-free survival and overall survival) and causes of death.	- Two-year OS was 100% for low-risk, 93% for medium-risk, and 91% for high-risk patients - OS for HIV-negative (93%) and HIV-positive (89%) patients were similar (p=0.53) - Total lymphocyte count $>0.6 \times 10^9$ predicted survival (94 vs 83%, p=0.02)	Risk stratification correlated with prognosis. Two-year OS of both HIV-positive and HIV-negative patients improved since 2010, partially ascribed to standardised treatment and increased supportive care.
6	To determine if changes in the levels (absolute levels and/or trends, alone and in combination) of haematological values and non-specific are associated with a PET-negative study after two cycles of first-line therapy.	- Optimal model had a predictive accuracy of 80% and a receiver operating characteristic (ROC) area under the curve (AUC) of 89%. - The most predictive variables were the differences in haemoglobin and ALC, each contributing 17% to the model. Differences in LDH and AEC contributed 15% and 14% respectively. Differences in TWC contributed 13%, while differences in ESR, ferritin, and albumin each contributed 6-9%.	Changes in low-cost, widely available blood tests may predict chemosensitivity for paediatric patients with cHL without access to PET-CT, identifying patients who may not require radiotherapy. Changes in these non-specific blood tests should be assessed in combination with clinical findings and available radiological imaging to avoid under-treatment.

Table 2. Consolidated study findings

Chapter 2 reports a 5-year OS of 84% for HIV-negative patients and 49% for HIV-positive patients. We hypothesised that certain factors would have prognostic significance in predicting 5-year OS. While univariate analysis found that age <10 years, HIV infection, advanced stage, B symptoms, African descent and treatment with ABVD-ChlVPP or OEPA/OPPA-COPP were associated with lower overall survival, only HIV infection, advanced stage and treatment regimen were confirmed as significant on multivariate analysis.

This historical perspective on patients in South Africa provided valuable baseline data to guide the choice of future chemotherapy. Before this study, there were no standardised treatment guidelines for South Africa, and each POU used protocols that they were familiar with. All protocols used were devised in high-income countries and were sometimes arbitrarily modified in each POU in a non-systematic manner. As an example, the POUs in the Wits circuit used OEPA/OPPA-COPP, a treatment guideline derived in Germany and used with great success to improve survival rates based on successive iterative study protocols. However, the analysis of retrospective data showed that OEPA/OPPA-COPP did not result in similarly high survival rates in the South African context and that treatment toxicity was responsible for a significant proportion of deaths in this group of patients. ABVD-ChlVPP, a regimen shown to have relatively high survival rates in the UK, also did not yield as high a survival rate as ABVD alone in our retrospective analysis and has been shown in other settings to be associated with a higher incidence of later secondary malignant neoplasms.⁷¹

Retrospective analyses are constrained by the inability to control exposure or outcome assessments and may be affected by various biases including selection, recall, misclassification and information bias and other inaccuracies.¹¹⁸ The survival rates were lower in some resource-constrained POUs, although the numbers were too small to confirm this with statistical significance. Nevertheless, the sample size of 294 patients was relatively large for a single country and provided valuable insights into treatment outcomes.

This study was the first collaborative project that included data from every POU in the country in a formal collaboration under the auspices of the South African Children's Cancer Study Group (SACCSG) now known as the South African Association of Paediatric Haematology Oncology (SAAPHO). The national retinoblastoma protocol project was launched in 2012 with

the participation of a selected number of POUs. It has produced valuable data, with certain results presented at national and international conferences, and retrospective data was included in global retinoblastoma studies, providing important insights into retinoblastoma presentations and outcomes on a global scale.^{119–121} A publication of purely South African retinoblastoma data is in progress and it is expected that the implementation of a prospective treatment protocol resulted in better outcomes.

* * *

In **Chapter 3** we explored the reasons for the lower 5-year OS in CAYA with HIV and cHL. In comparison with the HIV-negative patients, the HIV-positive patients were found to be younger, more likely to present with Ann Arbor Stage IV disease and more likely to present with wasting and stunting, all factors associated with poorer prognosis.^{122–124} The lower survival rate in HIV-positive patients was associated with an AIDS-defining CD4 percentage of less than 15% and hypoalbuminaemia of less than 20 g/dL. The deaths of CAYA with HIV were not, as expected, due to treatment-related toxicity but occurred later due to post-therapy opportunistic and nosocomial infections, prompting discussion about whether the combined immune dysregulation of HIV infection, chemotherapy and cHL contributed to this finding.

A difference between HIV-positive patients in the retrospective and prospective cohorts was that the majority patients diagnosed in the period 2000-2010 were not on antiretroviral therapy at the time of diagnosis with cHL, while those in the later cohort were. Despite the official rollout of antiretroviral therapy in October 2003, this was not easily accessible to many uninsured patients for years after the rollout.¹²⁵

Our study went beyond the standard 5-year follow-up period to document 10-year OS rates, an important contribution as most studies only report 5-year OS and this patient population faces a higher risk of opportunistic infections. Given that South Africa carries the highest HIV burden worldwide,¹²⁶ it was imperative for us to explore the underlying factors that contribute to the low OS observed among these patients. Although the numbers were small, this is nevertheless the largest cohort of CAYA with HIV and cHL that had been published.

* * *

The optimal approach for enhancing survival rates of patients with cancer entails the development of standardised treatment protocols, their effective implementation and the comprehensive analysis of treatment response with iterative changes to the subsequent research protocols. This has been done with great success in the UK, Germany, USA and other places.⁷² However, patients in the majority of sub-Saharan Africa countries have not benefited from this approach, with only a few studies being reported from Morocco,⁸⁴ Rwanda¹²⁷ and a consortium of Francophone African countries.⁴⁵ The creation of site-specific AMGs takes into account regional variations in healthcare resources, epidemiology, and access to specialised treatments. Such AMGs help healthcare providers make informed decisions about treatment options that are feasible and realistic within the local context.

Chapter 4 describes the successful implementation of a harmonised AMG in all South African POUs. Upper-middle-income South Africa occupies a unique place in Africa as it has the most unequal economy in the world with the highest Gini coefficient, a measure of economic inequality.¹²⁸ Other factors that make South Africa distinctive are the afore-mentioned large cohort of people living with HIV,¹²⁶ a highly trained healthcare workforce and subsidised, often free, access to specialised healthcare.¹²⁹ The modalities required for first-line management of cHL include diagnostic capacity, chemotherapy, pharmacy, nursing, paediatric surgery and radiotherapy. Before this study, the availability of these fundamental modalities was undocumented, and it was not known whether every POU had the capacity to treat children and adolescents using these modalities or whether they had the capacity to participate in a multicentre research study.

By surveying CRs before and during the study, I was able to conduct a broad assessment of possible challenges to successful implementation and identify potential solutions. The pre-study survey identified potential barriers to participation including time constraints and understaffing, while PET-CT was unavailable to two centres. CRs were then encouraged to transfer patients to other centres for PET-CT scans when possible, and the REDCap database was iteratively adapted to facilitate data capture and provided time-saving calculations and reference resources to make participation as easy as possible. Thus all state POUs met the minimum criteria to participate. The WhatsApp group encouraged dialogue and discussion of challenging cases and regular feedback was given both to individual CRs and to the whole group in formal meetings to encourage adherence to the study protocol and ensure quality data capture.

Major findings of the mid-study survey confirmed that the fundamental requirements were in place. Barriers to participation included time constraints, lack of dedicated research staff and excessive time to obtain regulatory approvals. These approvals prior to patient enrolment created barriers to study initiation and adoption (see “Reflections on HREC submissions and approvals” below).

The strengths of this study were that every POU participated in the feasibility surveys and that a single CR from each POU championed the project, answered all survey questions and implemented the prospective study in their individual POUs. CRs put aside personal preferences and adhered to a harmonised management guideline in order to answer important study questions, with the ultimate aim of improving survival rates.

Other challenges included loss of some CRs through retirement or change in interest, and these were replaced by others who had not been present since the start of the project. These new participants had to be inducted into the study and required regular contact.

Specific features in the REDCap database to facilitate timeous data entry and decrease workload included International Classification of Disease (ICD10) code finders, chemotherapy, body surface area and body mass index calculators. While many CRs expressed interest and commitment at the start of the study, and attended all in-person and online meetings, upon commencement of data entry they encountered challenges that impeded their ability to maintain a consistent pace. To address the issue, I opted to acquire digital versions of patient notes and personally input them. Additionally, I dispatched a research assistant to various POUs to retrain clinical researchers on accessing the REDCap database and accurately entering data. The Wits REDCap managers were always available to answer questions on REDCap and joined one of the in-person meetings to give detailed training on the use of the REDCap database.

Future modifications could include automated reminders and exploration of the other capabilities offered by REDCap. Automated reminders may improve the efficiency of data collection processes by reducing the likelihood of missed deadlines or overlooked tasks.¹³⁰ Consideration of other emerging technologies in data collection may also increase participation.

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Before the implementation of this AMG in South Africa, response evaluation was performed sporadically and inconsistently in many units, although this had become standard-of-care in high-income settings and PET-CT facilities were available to most POU's. Widespread adoption of this AMG resulted in the majority of patients undergoing response assessment with iPET-CT. A minority were assessed with CT only, mostly when PET-CT was unavailable e.g. when the machines were broken or when the 18-FDG was unavailable which happened consistently in December when facilities to produce this radioactive tracer shut down over the holiday period. This is a vast improvement from previous years when many patients completed a standard six courses of treatment without formal response assessment.

While the COVID-19 pandemic undoubtedly placed strain on the CRs and their POU's, they reported no negative effects on patient recruitment and treatment, in contrast to colleagues in other countries.^{131,132} This could be attributed to the fact that the study was integrated into routine care, with the only additional responsibilities being obtaining patient informed consent and recording data.

Despite the many obstacles, this part of the study demonstrated that multicentre collaboration and harmonisation of management protocols are indeed achievable in South Africa. Similar barriers identified by the Indian Paediatric Oncology Group (InPOG) included the necessity for multiple reminders to input data timeously, disagreements about radiation doses, fields and indications and occasionally restricted access to PET-CT.¹³³

* * *

Chapter 5 reports the results of the prospective introduction of a single harmonised protocol to South Africa. The study did not involve the use of novel or experimental agents and was observational in nature, aiming to introduce the concept of an adapted treatment regimen to South Africa, rather than the adoption of a regimen that may not be relevant in the middle-income setting.

The widespread adoption of risk stratification represented a refinement of the traditional Ann Arbor staging, in line with modern management of cHL in high-income settings.⁷² Patients thus received treatment tailored to their individual presentation. Risk stratification correlated with OS, confirming that this stratification had utility in the South African setting. HIV-positive patients were given additional supportive care in the form of filgrastim, which had not been implemented consistently before this study protocol, and could be treated with ABVD for all six cycles instead of ABVD for two cycles followed by COPDac for four cycles if high-risk, as COPDac was more myelotoxic in these patients.

Only one prognostic factor was identified as significant, namely a total lymphocyte count $>0.6 \times 10^9/L$, correctly predicting OS. Although most potential prognostic factors were not shown to be statistically significant, differences remain that may become significant with larger patient numbers. Alternatively, these results may suggest that adverse predictors may be largely overcome in patients receiving adequate multimodal therapy using risk stratification and response adaptation, as was posited as the ideal of treatment by Hasenclever in 2002.¹³⁴

* * *

Chapter 2 describes an improvement in the 2-year OS in comparison with the historical cohort, which we ascribe partially to the use of a standardised treatment protocol with clear guidelines on indications to delay therapy, decrease treatment intensity, enhance supportive care and consolidate with radiotherapy. Previous management regimens were more intensive and required hospital admissions. The adoption of less toxic, outpatient-based regimens may decrease treatment abandonment as there is increased convenience and lower morbidity.

Access to comprehensive treatment guidelines enhances medical practice by promoting adherence to established protocols and preventing unnecessary delays, improvisation or deviations in the clinical decision-making process. They provide a structured framework and evidence-based recommendations that enable healthcare professionals to make informed and consistent choices, thereby optimising patient care outcomes.¹³⁵ However, it is important to acknowledge that this positive trend may also stem from improved accessibility to healthcare services and evolving demographic patterns.

The improved 2-year OS of 89% in the prospective cohort of CAYA with HIV and cHL, in comparison with 65% in the retrospective cohort (see Chapter 3) is encouraging. This change could indicate advancements in the management of CAYA with both HIV and cHL and the implementation of knowledge gleaned from the retrospective study. Additionally, the reduction in stigma surrounding HIV and the increased availability of antiretroviral therapy may have contributed to this improvement.¹³⁶ It is possible that, with our modified approach to the management of CAYA with cHL and HIV, these patients may experience better long-term survival. However, it is important to ensure that these patients receive regular follow up and meticulous monitoring for opportunistic infections to prevent the mortality observed in the five and ten year period post diagnosis.

The main aim of this project was to improve survival rates of CAYA with cHL and this was achieved, representing successful implementation of this model. While participants enrolled in randomised controlled trials and clinical studies often demonstrate favourable survival rates, a definitive systematic review yielded inconclusive evidence to support the widely cited notion of clear benefits of enrolment in such studies.¹³⁷

* * *

Although PET-CT is now available to most South African patients, this modality, currently considered standard-of-care for interim assessment of cHL in well-resourced settings, is inaccessible to the vast majority of patients in Africa.³³ In addition, as noted in Chapter 4, PET-CT is occasionally unavailable in South African centres. As members of the African community with access to resources that most do not have, we are ideally placed to devise creative solutions to address this problem. While we ourselves cannot assist with increasing access to this expensive nuclear medicine modality, we can leverage our data and resources to determine whether there are surrogate markers that can be used to predict interim response.

Chapter 6 describes the results of the different models used to analyse correlations between changes in blood markers with interim assessment by PET-CT. The bundle of tests cost

approximately R2000 in 2018 at the start of the study, in contrast with R30 000 for a PET CT scan.

The choice to analyse changes in non-specific markers and certain haematological parameters was informed by multiple reports of the prognostic capacity of single makers to predict overall survival. Copper was included in the bundle as it was available in the local setting, was still being used in some centres, and had not been assessed in any African setting. At the time of writing, data from 160 patients had been uploaded on the REDCap database, data from 132 was complete enough for survival analysis, and 96 patients had had both baseline and interim PET-CT performed. This was considered sufficient to include in the analysis by ROC curves and other calculations as the minimum required paired datasets was calculated to be 42.

The main findings of this study were that changes in certain haematological values and non-specific markers may predict chemosensitivity for paediatric patients with cHL. This may be useful for patients in resource-constrained settings without access to PET-CT, thus identifying patients who may not require radiotherapy.

Although the current findings are encouraging, their clinical utility remains limited. To facilitate practical application, we envision a formula, scoring system or mobile application for easy use in the clinic to assess the significance of changes in blood tests for individual patients. We aim to develop such a tool that utilises patient-specific data to predict chemosensitivity, similar to the approach undertaken by Wallace *et al.*¹³⁸ in their prediction of ovarian failure after local radiation. (The tool can be viewed here: <https://tom.host.cs.st-andrews.ac.uk/radiosensitivity.html>) This endeavour requires a sufficient number of patients to be enrolled, ensuring comprehensive data collection and validation for the development of a reliable and practical tool. By leveraging technological advancements, such as a user-friendly mobile application or a streamlined formula, we may be able to enhance the effectiveness of clinical assessments in real-time scenarios, even in resource-constrained settings.

Reflections on HREC submissions and approvals

Serious ethical violations involving falsified data¹³⁹ and exploitation of vulnerable populations have occurred in Africa: inadequate informed consent processes, unreported severe adverse events and harm to patients as a result of their participation in clinical trials are well documented.¹⁴⁰ Clearly, it is essential to protect vulnerable patient populations and ensure academic rigour. In cases where an intervention, such as ABVD-COPDac, is widely recognised as the standard of care or best practice, and the study is based on observational data rather than experimental agents, the existence of fragmented bureaucracy does not facilitate the promotion of ethical research. Instead, it serves as an obstacle to the smooth implementation of such studies. Resources are expended in the repeated review of the same study protocol across multiple institutions, in a setting that is already resource-constrained.

For the retrospective component of this study, ethics committee approval was granted by ethics committees of eight academic institutions for the retrospective component. For the prospective component, we received approval from 15 academic institutions and three private hospitals and registered the study on nine provincial research databases and the national human research database. Each application took months to process, in one instance 18 months. At least one private-sector CR did not pursue participation in the study due to the perception of an overly stringent process.

Despite the theoretical promise of reciprocal approvals, in practice, a new full application had to be submitted at every institution. Participation of each POU necessitated a separate and distinct application process, even if the study had already received approval at institutions such as the University of the Witwatersrand and other universities. In one university, the study had to be approved by a scientific committee before being submitted to the ethics committee, despite being approved by the Wits Postgraduate Committee.

Requirements varied around the country: some required translations of patient information sheets and informed consent and assent forms into local languages, while others did not. Some required extensive justification of the inclusion of race (however defined) in the demographic data collected, while the majority did not. The application process and the designated points of contact within several institutions lacked clarity, causing confusion and ambiguity. Transitions of leadership within the human research ethics committees resulted in shifting requirements and guidelines, causing disruptions and alterations to the application process during its course.

While ethics committee and hospital approval was attained for all POUs, in practice the CRs did not have time to submit the necessary documentation as they are all part of high-intensity, understaffed POUs. As the national PI, I took on the task of applying for and acquiring the necessary approvals, as well as registering the study on the national and provincial research health databases. Consequently, I faced the burden of repeating the application process for each POU independently, which not only consumed additional time and resources but also hindered the overall progress of the study.

The divergence from the concept of reciprocal approvals underscored the need for improved coordination and harmonisation among institutions involved in paediatric oncology research. Establishing a standard operating procedure for acknowledging and accepting approvals from reputable institutions would alleviate redundant administrative efforts and facilitate a more cohesive and expedited research process.

Efforts should be directed toward fostering a collaborative environment that promotes mutual recognition of approvals, eliminating the need for redundant applications and allowing research initiatives to progress smoothly across different POUs. This could be achieved through enhanced communication, shared guidelines, and the development of a coordinated framework that upholds the principles of reciprocal approvals while ensuring the protection of ethical standards and patient welfare.

HREC members have varying levels of expertise in assessing paediatric cancer study protocols. This discrepancy in expertise among HREC members can introduce challenges and inconsistencies in the review process. The complexity of paediatric cancer research necessitates a thorough understanding of the unique ethical considerations and nuances involved. Assessing the risks and benefits, ensuring the protection and welfare of child participants, and evaluating the appropriateness of study design require a comprehensive understanding of paediatric oncology. Conversely, members with specialised knowledge may be better equipped to identify potential ethical issues and propose appropriate safeguards.

To ensure robust and comprehensive ethical review of paediatric cancer studies, it is essential to consider the expertise and composition of HREC members. Adequate representation from experts in paediatric oncology or related disciplines can contribute to a more informed

evaluation process, fostering ethical research practices and safeguarding the welfare of child participants. Additionally, providing ongoing training and education to HREC members on paediatric cancer research can help bridge knowledge gaps and promote consistent, well-informed decision-making. This may be achieved by creating a centralised cancer ethics committee, similar to that created in Canada in 2004.¹⁴¹ The Ontario Cancer Research Ethics Board, covering a population of 12 million people, positioned itself as a centralised, cancer-specific institutional review board to streamline expert review. Soon after its launch, this entity reported success in reviewing and approving more studies more quickly.¹⁴²

Although the volume of cancer-specific studies conducted in South Africa may not be substantial enough to warrant the establishment of a dedicated specialised ethics committee,¹⁴³ the idea of a regional ethics review committee with expedited approval from affiliated individual sites holds merit. By consolidating the regional expertise and perspectives of diverse stakeholders, this committee could streamline the review process and provide a comprehensive evaluation of research proposals. Such a committee, perhaps convened on an ad hoc basis, could leverage the collective knowledge and experience of members from various sites. This collaborative approach can enhance the quality and consistency of ethics review, ensuring that research protocols meet the necessary ethical standards and align with local contextual considerations. Furthermore, the involvement of affiliated individual sites in the approval process could expedite the review timeline, enabling the timely initiation of research projects.

Reflections on current best practice in LMIC

Through my involvement in the development of harmonised guidelines for paediatric cHL in sub-Saharan Africa, a process supported by the National Comprehensive Cancer Network (NCCN) and funded by the American Cancer Society,¹⁴⁴ I gained useful insights into the limitations of such processes. The harmonised guidelines for sub-Saharan Africa largely align with those for the United States, positioned as the epitome of best practice without taking into account the resources and capacities available in local settings. Sub-Saharan Africa encompasses a population of nearly 1.5 billion people,¹⁴⁵ characterised by considerable variations in wealth and healthcare capacity across different regions. Hence, it is impractical to apply a uniform guideline across the entire region without considering the specific contexts and realities of each local setting.

Another valuable initiative is the Adapted Resource and Implementation Application (ARIA) Guide, positioned as “a comprehensive online clinical resource aimed at providing tailored guidance for the treatment of childhood and adolescent cancers on a global scale”.¹⁴⁶ While undoubtedly serving a crucial purpose, these guides inherently face limitations in their ability to cater to the specific needs of every setting, and should be viewed as offering a broad overview of potentially beneficial approaches within resource-constrained contexts.

Partners in HIC may have access to well-funded and adequately resourced healthcare systems. Guidelines developed in such contexts may not consider the limited resources characteristic of LMICs, making them impractical or unsustainable. Both the ARIA and the NCCN guidelines were initially conceptualised in the United States and are primarily led by partners from high-income countries. These arrangements arise out of necessity, as partners from LMIC often lack the necessary resources to spearhead such ambitious projects. Designing guidelines tailored to the specific context of LMICs ensures that recommendations are relevant and feasible within the local healthcare system. It thus becomes necessary for clinician-researchers (CR) in countries such as South Africa to initiate more detailed projects in their own regions to ensure relevance and applicability.

Recommendations

Building upon the success of a harmonised treatment guideline for paediatric cHL, it is crucial to develop and implement guidelines for the remaining WHO index cancers in South Africa. These include retinoblastoma, low-grade glioma (both in process), acute lymphoblastic leukaemia, Burkitt lymphoma and nephroblastoma.¹⁵ Numerous studies have demonstrated the efficacy of AMG in LMICs.^{37,45,84,147,148} In the quest to achieve the ambitious targets of the WHO GICC of doubling global survival rates to 60%, it is essential that South Africa, other countries and cooperative groups implement AMG tailored to their specific contexts while adhering to accepted standards of care. The obvious next step will be to analyse and disseminate the results of AMG implementation, ensuring sufficient patient numbers to draw conclusive findings.

For CAYA with HIV and cHL, risk-stratified and response-adapted therapy, supplemented by additional supportive care, should be provided. The option to de-intensify treatment when deemed necessary is essential. Once the outcomes of more patients are analysed, we aim to establish management guidelines for the management of Hodgkin lymphoma in children and adolescents with HIV infection.

Considering the progress made, it would be advantageous to establish a regional cooperative group in sub-Saharan Africa. This collaborative effort would foster continued research, enabling iterative studies to build upon the successes achieved thus far. Suggestions for inclusion in the next study protocol involve considering the use of more intensive chemotherapy combinations such as BEACOPP or COPDAC as upfront therapies for high-risk patients and devising an algorithm for relapsed and refractory cases. In cases of relapsed and refractory disease, histological confirmation should be obtained to obtain the most accurate evaluation of treatment-resistant cHL. Although BEACOPP and COPDAC are associated with higher rates of toxicity, options such as brentuximab-vedotin, bendamustine and pembrolizumab are prohibitively expensive in the state sector, and currently difficult to access in the private sector due to inability or unwillingness of medical insurance companies to fund them. However, the option of investigator-led, pharma-funded studies is a possibility that could be explored.

Integrating research into clinical practice is of paramount importance. Rather than solely adopting protocols from other regions, South Africa should invest in conducting local research. Hence, it is vital to cultivate disease-specific expertise among CRs and embrace a collaborative

approach that promotes seeking advice and guidance from local experts rather than striving to become authorities in every field. To foster collaboration and participation, it is necessary to encourage multi-authored papers using established authorship criteria.¹⁴⁹ By doing so, individuals may be incentivised to contribute and expand their knowledge and expertise.

By emphasising the integration of research into clinical practice, conducting locally relevant research and promoting collaboration, the South African paediatric oncology community can enhance its ability to develop and implement effective treatment guidelines for various cancers. This approach not only improves patient outcomes but also facilitates the growth of a robust research community. In comparison with HIC, there are minimal published prospective research studies on childhood and adolescent cancers from the African continent.¹⁴³ South African data on childhood and adolescent cancers offers a unique perspective due to the country's diverse population and healthcare challenges. South Africa's contribution to childhood and adolescent cancer data not only benefits the country's healthcare system but also serves as a valuable resource for the international community.

Limitations

The retrospective nature of the initial phase of the study (Chapters 2 and 3) introduces the potential for recall bias and incomplete data. The reliance on historical medical records and retrospective data collection may have resulted in incomplete or inconsistent information, affecting the overall robustness of the findings.

While efforts were made to adhere to the study protocol in the prospective part of the study (Chapters 4-6) it is important to acknowledge that this study operates more as a guideline and observational study rather than a strict research protocol where patients might be removed from study in the event of the protocol violations. As a result, there might be variations in treatment delivery and adherence to the defined protocol, which could introduce confounding factors and impact the observed outcomes (Chapter 5). However, the value of observational and clinical practice data includes assessments of how interventions perform in clinical settings and a more reflective diversity of patients.¹⁵⁰

The inherent limitations of comparing retrospective data with prospective studies (Chapter 2 and 5) are acknowledged. Prospective studies, with their predefined methodologies and systematic data collection, generally offer more reliable results compared to retrospective analyses. The limited number of participants included in the study may affect the generalisability and statistical power of the findings (Chapter 6). It is important to interpret these results within the context of the sample size and exercise caution when drawing definitive conclusions or making broad generalisations based on the limited number of patients studied.

Despite these limitations, the findings from this study provide valuable insights and serve as a foundation for future research. Further investigations with larger sample sizes and prospective designs would be beneficial to confirm and expand upon the findings of this study.

Strengths

This study represents an advance for paediatric oncology in sub-Saharan Africa, as it pioneers the design and implementation of a widely adopted, national harmonised treatment guideline. Using retrospective baseline data from a comprehensive cohort of nearly 300 patients, we meticulously analysed the data to inform the development of a prospective study protocol, ensuring that we had carefully examined all local factors including the relatively high prevalence of HIV infection.

This study is the first of its kind in sub-Saharan Africa to document the successful implementation of a national harmonised management guideline incorporating both risk-adjusted chemotherapy and response-directed radiotherapy for paediatric patients with cHL. In this AMG, we introduced the use of the more contemporary risk stratification, an advance from the traditional Ann Arbor staging system, without incurring extra costs. Our approach aimed to mitigate the potential late effects of radiotherapy by encouraging the use of more sophisticated techniques, although we may only see these benefits in future decades. We showed that multicentre collaboration was not only possible but successful, and was associated with improved survival rates, most strikingly in CAYA with HIV and cHL. For this project, individual CRs set aside personal practice preferences and committed to a single AMG to answer important clinical questions, with encouraging results.

By capturing observational data from diverse patient populations, this study offers insights that are not artificially controlled, making the results generalisable in similar middle-income settings and applicable to real-life clinical scenarios. Unlike controlled experimental studies, observational studies provide a broader representation of the patient population and their associated complexities, allowing for a more accurate understanding of treatment effectiveness and outcomes in real-world settings. In addition, these findings may be useful for settings that do not have access to PET-CT facilities.

The inclusion of patients from both the public and private sectors, within a society characterised by wide socioeconomic disparities, enhances the generalisability of the findings. Notably, this study represents the first instance where all public sector POUS and a majority of private sector

practitioners have adopted such an approach and is in accordance with the GICC approach, marking the implementation of these principles in the comprehensive management of one of the six tracer cancers in South Africa. The implications of the study results extend beyond cHL, as they hold relevance for future treatment guidelines in various malignancies. The establishment of standardised adapted management guidelines assumes particular significance as South Africa progresses in the development of the National Health Insurance Plan.

Conclusion

Our retrospective, multicentre study documented 5-year OS rates of 84% in HIV-negative patients and 49% in HIV-positive patients with cHL, showing that ABVD was associated with higher survival rates than more toxic chemotherapy combinations. We demonstrated the feasibility of introducing a national harmonised treatment guideline and showed efficacy with an improved survival rate of 93% in HIV-negative and 89% in HIV-positive patients. We further demonstrated that changes in a combination of low-cost, widely available blood tests correctly predicted chemosensitivity, identifying patients who may not require radiotherapy. In settings that do not have access to PET-CT, changes in affordable blood tests may be used to substitute for radiological interim assessment, although a format suitable for individual patients is yet to be developed for the clinical setting.

With this study, improvements in the survival of CAYA with cHL have now been documented in a South African population. While similar survival rates were already observed in the 1960s and 1970s, it has taken several decades to achieve such results in South Africa. Various factors might have contributed to these delays, including disparities in healthcare infrastructure, limited access to advanced treatments, financial challenges and other socio-economic factors.

The ongoing debate about whether to adopt intensive or less toxic treatment approaches has shifted over time. The medical community has oscillated between more and less aggressive treatment strategies in an attempt to strike the right balance between effectiveness and minimisation of side effects. Our findings demonstrate that patients with high-risk disease and comorbidities such as HIV infection can achieve high survival rates without subjecting them to excessively toxic therapies. This represents an advance towards personalised medicine, where tailored treatment plans are designed to address individual patient needs and health conditions, maximising the chances of successful outcomes while limiting the potential risks and side effects associated with treatment.

Integrating research into clinical practice is vital to achieve the highest survival rates possible within resource-constrained environments. The model of documenting baseline retrospective outcomes from multiple centres to inform prospective studies is extremely useful in settings

that do not have adequate registry data that includes both epidemiological data and mortality data. Collaborative studies such as this one are more likely to yield robust and generalisable results due to the relative rarity and complexity, increasing sample size by accruing more patients. Collaborative efforts allow for the integration of multidisciplinary knowledge and increasing diversity of the studied population. They facilitate resource-sharing, reducing the financial burden on individual institutions and accelerating progress by avoiding duplication of efforts.

Appendices

Appendix A. Staging

All patients were staged clinically and radiologically as per the Cotswolds-modified Ann Arbor staging system:

Stage I	involvement of a single lymphatic site (I) or localised involvement of a single extra lymphatic organ or site (IE).
Stage II	involvement of two or more lymph node regions on the same side of the diaphragm (II) or localised involvement of a single extra- lymphatic organ/site and involvement of one or more lymph node regions on the same side of the diaphragm (IIE)].
Stage III	involvement of lymph node regions on both sides of the diaphragm (III), which may also be accompanied by extralymphatic involvement associated by adjacent lymph node involvement (IIIE) or by involvement of the spleen (IIIS) or both (IIIE, S).
Stage IV	disseminated involvement of one or more extralymphatic organs, with or without associated lymph node involvement; or isolated extralymphatic organ involvement with distant nodal involvement. Stage IV includes involvement of the liver, bone marrow and/or lungs.

The Ann-Arbor classification is further subdivided using symptoms and modes of presentation:

A symptoms:	Lack of 'B' symptoms
B symptoms:	Presence of at least one of: unexplained recurrent fever >38°C; recurrent drenching night sweats; unexplained loss of > 10 % body weight in the preceding 6 months
X:	Bulky disease defined as more than 6cm in any axis or more than 33% of the cardiothoracic diameter on chest X ray.
S:	Splenic involvement, based on CT, MRI or PET-CT findings
E:	Involvement of a single extra-nodal site that is contiguous or proximal to the known nodal site.

Appendix B. Risk stratification

Risk stratification for children, adolescents and young adults on the SACCSG-HL-2018 study

Standard risk	Medium risk	High risk
Stage I (A and B)	Stage I with risk factors • bulky disease X or • extra-nodal disease E	
Stage IIA	Stage II with risk factors • bulky disease X or • extra-nodal disease E	Stage II with both • bulky disease X and • extra-nodal disease E
	Stage IIIA	Stage III with risk factors • B symptoms • bulky disease X • extra-nodal disease E
		Stage IV

Appendix C: Essential requirements for POU to participate in study

ESSENTIAL

1. At least one qualified paediatric oncologist or paediatric haematologist, in the case of children and adolescents under the age of 18 years.
2. At least one qualified medical oncologist, clinical haematologist or clinical oncologist, in the case of patients aged 18-22 years.
3. Member of South African Children's Cancer Study Group (SACCSG), South African Society for Clinical and Radiation Oncologists (SASCRO) or South African Society of Medical Oncology (SASMO). (These will be confirmed by the PI as individual investigators join the project, in the case of physicians who treat adults.)
4. Basic X ray facilities to perform chest X rays.
5. PET CT scanning facilities. These may be on site or at the closest referral hospital and patients must be able to have a PET-CT within one week of presentation.
6. Ability to perform core biopsies or excision biopsies within one week of patient presenting to centre.
7. Histopathology services (National Health Laboratory Services).
8. Chemotherapy for first line therapy (adriamycin, bleomycin, vinblastine, dacarbazine).
9. Chemotherapy for intensified treatment (cyclophosphamide, vincristine, prednisone, dacarbazine).
10. Functioning pharmacy with the capacity to mix chemotherapy
11. In-patient facilities for patients who require it (those who develop complications requiring hospitalisation and those who receive COPDac).
12. Radiotherapy facilities able to perform involved field radiation.
13. Internet access
14. Training in REDCap data capture

PREFERABLE

15. At least one oncology-trained nursing staff member per shift.
16. Multidisciplinary team meetings preferable but not essential.

Appendix D. Pre-study questionnaire

Data Dictionary Codebook SACCSG-HL-2018 feasibility

1. How many full time consultants work in your primary unit?
Primary unit refers to the hospital where you spend the majority of your time.
2. How many registered paediatric haematologists/ oncologists work in the unit?
3. How many fellows/ senior registrars are assigned to your unit?
4. How many medical officers are permanently assigned to your unit?
5. How many new oncology patients per year are treated in your unit?
6. Do you have access to ABVD medications? (Adriamycin, bleomycin, vinblastine, dacarbazine) Please choose the option that is most accurate in your setting
 - 0% of the time
 - 50% of the time
 - 75% of the time
 - 100% of the time
7. Do you have access to COPDac medications? (Cyclophosphamide, vincristine, prednisone, dacarbazine)
Please choose the option that is most accurate in your setting.
 - 0% of the time
 - 50% of the time
 - 75% of the time
 - 100% of the time
8. Do you have access to ICU care for patients with Hodgkin lymphoma
Please choose the option that is most accurate in your setting.
 - 0% of the time
 - 50% of the time
 - 75% of the time
 - 100% of the time
9. Do you have regular multidisciplinary team discussions?
 - Yes
 - No
10. Is there access to radiotherapy within a reasonable distance from your unit?
Please choose the option that is most accurate in your setting
 - None
 - Up to 25% of the time
 - Up to 50% of the time
 - Up to 75% of the time

100% of the time

11. What type of radiotherapy is available for the treatment of HL patients? (Within reasonable distance from your unit)
- Involved-field radiotherapy
 - Involved-site radiotherapy
 - Involved-node radiotherapy
12. Do you have access to appropriate radiological services, including review/ reports?
Please check all that apply.
This question does not relate to PET scans.
- None
 - Chest X ray
 - CT scans
 - MRI
13. Do you have access to PET scanning facilities for patients with HL?
- Yes
 - No
14. What barriers or challenges do you foresee in taking part in the SACCSG-HL-2018 study?
Please be as frank as you can.
15. Please record any potential solutions you can think of to solve these potential problems.
16. If we were to access more funding for this project, are there any specific things you would like funded to assist you to take part in this project?
Please record as much detail as you think would be helpful.
17. Please record any particular comments or suggestions that you believe should be taken into account to make this project a success?
Feel free to be as detailed as you wish.

Appendix E. Mid-study questionnaire

1. Oncology trained nurse/s per shift
 - a. At least one oncology trained nurse per day shift
 - b. More than one oncology trained nurse per day shift
 - c. No oncology trained nurses per day shift
2. Supplementary staff available (includes research assistants, data capturers, data managers)
 - a. No supplementary staff available
 - b. Supplementary staff available
3. Multidisciplinary team (MDT) meetings
 - a. We do not have any MDT meetings
 - b. We participate regularly in MDT meetings in our centre
 - c. Other
4. Which changes would you suggest to make this study easier to participate in?
 - a. (Free text)
5. Have any patients you have approached declined to participate?
 - a. Yes
 - b. No
 - c. Not applicable
6. How many patients who are eligible to participate in this study have not been enrolled?
 - a. Free text (number)
7. Have you completed a Good Clinical Practice or other ethics course in the last five years?
8. Any other comments or concerns?
 - a. Free text

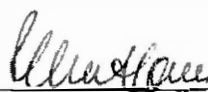
Appendix F. Wits HREC approval (retrospective)



R14/49 Dr Jennifer Geel et al

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

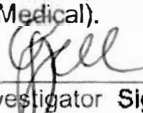
CLEARANCE CERTIFICATE NO. M160770

NAME: Dr Jennifer Geel et al
(Principal Investigator)
DEPARTMENT: Paediatrics and Child Health
Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE: Hodgkin Lymphoma in South African Children and Adolescents from 2000-2010: A First Report by the South African Children's Cancer Study Group (SACCSG)
DATE CONSIDERED: 29/07/2016
DECISION: Approved unconditionally
CONDITIONS:
SUPERVISOR:
APPROVED BY: 
Professor P. Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL: 02/10/2017

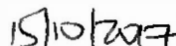
This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 10004, 10th floor, Senate House/3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/We fully understand the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit to the Committee. **I agree to submit a yearly progress report.** The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed July and will therefore be due in the month of July each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).


Principal Investigator Signature

Date


15/10/2017

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

R14/49 Dr Jennifer Geel

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M1711100

NAME: Dr Jennifer Geel
(Principal Investigator)
DEPARTMENT: Paediatrics and Child Health
Charlotte Maxeke Johannesburg Academic Hospital
Chris Hani Baragwanath Academic Hospital
Wits Donald Gordon Medical Centre

PROJECT TITLE: The feasibility of introducing a harmonised treatment regimen comparing affordable blood tests and PET CT scans to improve two year survival rates in children, adolescents and young adults with Hodgkin Lymphoma in South Africa

DATE CONSIDERED: 24/11/2017

DECISION: Approved unconditionally

CONDITIONS:

SUPERVISOR: Prof Daynia Ballot

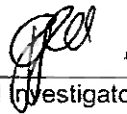
APPROVED BY: 
Doctor CB Penny, Chairperson, HREC (Medical)

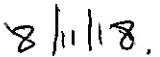
DATE OF APPROVAL: 24/10/2018

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary, Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report.** The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **November** and will therefore be due in the month of **November** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).


Principal Investigator Signature


Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix H. Consent form

INFORMATION SHEET FOR CONSENT

PATIENTS/PARENTS/GUARDIANS

Study title:

The feasibility of introducing a harmonised treatment regimen, comparing affordable blood tests and PET CT scans, to improve two year survival rates in children, adolescents and young adults with Hodgkin lymphoma in South Africa

Good day. My name is Dr. Jennifer Geel. I am currently working in the Division of Paediatric Oncology, Charlotte Maxeke Johannesburg Academic Hospital. Permission to conduct this study has been granted by the Wits Human Research Ethics Committee.

Introduction

Doctors who treat Hodgkin lymphoma in children, adolescents and young adults in South Africa are doing research on Hodgkin lymphoma. Research is simply the process of learning the answer to a question or learning more about something. In this study we want to learn whether changes in certain blood tests can give us the same information about your response to treatment as a PET-CT scan. We would like to find out if we can learn the same information about response to treatment from a group of affordable and convenient tests as can be obtained from a PET-CT scan. The findings from this study may help us to decide if changes should be made to the standard treatment and tests for Hodgkin lymphoma. We would like to request your permission to included anonymised data about your/your child's condition in this study.

Invitation to participate

We are asking for your permission to include your/your child's data in this research study. We would like to include data relating to your/your child's treatment in a nationwide study to improve care for children, adolescents and young adults with Hodgkin lymphoma in South Africa.

What is involved in the study

This is an observational study. You/your child will be receiving standard chemotherapy for this condition. This is ABVD chemotherapy (adriamycin, bleomycin, vinblastine and dacarbazine) which is a well-known combination, followed by radiation if we have any concerns that there might have been inadequate response to the chemotherapy or if there are certain high risk features. After two to three cycles of chemotherapy (two to three months), we will check to see if you/your child have/has responded well to the treatment. If the response is not as good as we had hoped, you/your child will receive radiotherapy at the end of the chemotherapy. If you/your child have/has high risk disease, you/your child will receive more intensive COPDac chemotherapy (cyclophosphamide, vincristine, prednisone, dacarbazine). Once this treatment is completed, we will again reassess.

There is no experimental treatment in this study. Once all the treatment has been completed, we will continue to monitor you/your child closely to pick up any possible signs of relapse (the cancer coming back) or side effects from the chemotherapy and/or radiotherapy. The intention of the study is to follow your/your child's progress through the treatment and then after treatment to at least five years from the end of therapy. This is to ensure that any complications which may arise at a later stage can be detected early and that appropriate help can be offered.

As part of standard treatment, you/your child will require a combination of the following tests: blood tests, X-rays, PET-CT scans, ultrasound, CT scans and/or magnetic resonance imaging (MRI), depending on what is available at your/your child's hospital. The blood tests will require no more than 10mL of blood (2 teaspoons) at the start of each cycle of chemotherapy, six times in total. All of these tests have to be done to treat your/your child's cancer, even if you/your child are/is not on a study. There will be no extra tests or hospital visits required to take part in this study.

You are free to withdraw your consent to participate in the study at any point. You/your child will still receive the best possible care whether you/your child choose/s to stay in the study or to leave.

We expect that there will be at least 30 patients a year who are treated according to this protocol in South Africa. They will be children, adolescents and young adults. All procedures will be performed in the same hospital where you/your child will be treated, unless you/your child are/is referred to another hospital if certain tests are unavailable.

The study involves no additional risk or discomfort.

Costs of being in the study

All therapy will be paid for either by the state, according to a scale of benefits determined by the state or by your fund holder (medical aid), if you have one. The study itself does not incur any additional costs to you.

Benefits of being in the study

The benefits of being in the study are that your/your child's progress will be closely monitored, all tests and imaging (scans, X-rays) will be reviewed by a central committee to ensure accuracy.

Results of the study

You will be given pertinent information on the study while involved in the project and after the results are available.

Participation is voluntary, if you wish not to participate, there won't be any penalty or loss of benefits to which you/your child are/is otherwise entitled.

Confidentiality

All efforts will be made to keep personal information confidential. Absolute confidentiality cannot be guaranteed. Personal information may be disclosed if required by law. Organisations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the Research Ethics Committee (REC). Your/your child's name or identifying information will not be published in any medical journal or on the internet.

Contact details of researcher/s for further information / reporting of study related problems.

Dr. Jennifer Geel
Area 294, Charlotte Maxeke Johannesburg Academic Hospital
Jubilee Road, Parktown
011 488 3294/ 4292
jennifer.geel@wits.ac.za

Contact details of REC administrator and chair – for reporting of complaints / problems.

Prof. Clement Penny
clement.penny@wits.ac.za

Thank you for taking the time to consider our request.

Please sign to indicate that you have read and understood this document, and that the study has been explained to you in a way that you understand.

Signature of Patient

Date

Signature of Researcher

Date

Signature of Witness

Date

Please indicate if an interpreter assisted in this process.

Appendix I. Assent form

PARTICIPANT INFORMATION LEAFLET AND ASSENT FORM

TITLE OF THE RESEARCH PROJECT: Hodgkin lymphoma study

RESEARCHER'S NAME: Dr Jennifer Geel

ADDRESS: Area 294, Charlotte Maxeke Johannesburg Academic Hospital, Jubilee Road, Parktown

CONTACT NUMBER: 011 488 3294/ 4292

What is RESEARCH?

Research is something we do to find new knowledge about the way things (and people) work. We use research projects or studies to help us find out more about disease or illness. Research also helps us to find better ways of helping, or treating children who are sick.

What is this research project all about?

Doctors who treat Hodgkin lymphoma in young people in South Africa are doing research on Hodgkin lymphoma. Research is a way of learning the answer to a question or learning more about something. In this project we want to learn whether changes in certain blood tests can give us the same information about your response to treatment as a PET-CT scan.

Why have I been invited to take part in this research project?

You have been invited to take part in this project because you have Hodgkin lymphoma, which is a serious illness of the lymph nodes (glands) in your body. We will give you treatment to stop the growth. This means that we want to make you better.

Who is doing the research?

Dr Jennifer Geel from the Department of Paediatrics and Child Health, Charlotte Maxeke Johannesburg Academic Hospital and Dr _____ who is treating you in a team. In the team are doctors, nurses and social workers.

What happens on standard treatment?

The study will be looking at what happens to you when having standard treatment for Hodgkin lymphoma. You will be treated with medicine called chemotherapy to make your cancer go away. This medicine will be given to you in a drip or a port. Once you have started the treatment, we will see if the cancer is getting smaller by doing scans and taking a small amount of blood. You may also get radiotherapy, which is a bit like having an X-ray.

What will happen to me in this study?

The study involved looking at all the results of your blood tests to see if they give us the same results as the PET scans. There are no additional blood tests required if you join this study.

Can anything bad happen to me?

No, nothing bad can happen to you from joining the trial as you will not be having any additional blood tests, procedures or hospital visits.

Can anything good happen to me?

The medicine we give you will hopefully make your cancer go away so that you will be healthy again. It will also mean that once you feel better you will be able to see friends and be able to go back to school.

Will anyone know I am in the study?

The data will be kept confidential, which means nobody but the treating doctor will know who you are. Your name will not appear on the data sheet where we look to see whether you have become better.

Who can I talk to about the study?

You can speak to anyone in our unit but your doctor or your parents may be the best people to start off with. Feel free to ask any questions at any time from whichever person you feel most comfortable with. Sometimes writing down questions can help us to remember what to ask.

You can call Dr Jennifer Geel on 011 488 3294 or email her on Jennifer.geel@wits.ac.za if you have any questions about the study.

What if I do not want to do this?

You can choose whether or not you want to be in the study. If you say “yes” we can collect your information about how you respond to the treatment. We will use this information to help other children with the same cancer. If you say “no” you will still get the same treatment and care from us.

Do you understand this research study and are you willing to take part in it?

☐ YES☐ NO

Has the researcher answered all your questions?

☐ YES☐ NO

Do you understand that you can pull out of the study at any time?

☐ YES☐ NO

Signature of Child

Date

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by Kebashni Thandrayen

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Appendix K. Declaration of contributions

Declaration of the contribution of the PhD candidate to the writing of each multi-authored paper

I, Jennifer Ann Geel, hereby declare the following:

I conceptualised this thesis with my supervisors. I developed the study protocol, including the development of the management algorithm, choice of chemotherapy, doses of radiotherapy, formulation of the questionnaires, writing of standard operating procedures and data collection. I trained the research assistants and collaborating clinician-researchers in data collection and capture, and was available to discuss challenging cases, assisting them to make appropriate treatment decisions. I performed data capture of the patients in the Wits circuit, as well as those in certain centres who experienced challenges. I recruited the patients at two hospitals and undertook all quality control of data management and worked with the collaborating statisticians. I wrote the five articles for publication and worked with the co-authors to achieve consensus on articles to be submitted for publication.

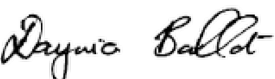
All authors have agreed to the use of these papers within the thesis.

Name of candidate: Jennifer Geel

Signature: 

Date: 08/12/2023

Name of supervisor: Prof Daynia Ballot

Signature: 

Date: 08 December 2023

Name of supervisor: Prof Monika Metzger

Signature: 

Date: 7.12.2023

References

1. Howard SC, Davidson A, Luna-Fineman S, et al. A framework to develop adapted treatment regimens to manage pediatric cancer in low- and middle-income countries: The Pediatric Oncology in Developing Countries (PODC) Committee of the International Pediatric Oncology Society (SIOP). *Pediatric Blood and Cancer*. 2017;64(November):1-18. doi:10.1002/pbc.26879
2. Flerlage JE, Kelly KM, Beishuizen A, et al. Staging Evaluation and Response Criteria Harmonization (SEARCH) for Childhood, Adolescent and Young Adult Hodgkin Lymphoma (CAYAHL): Methodology statement. *Pediatr Blood Cancer*. 2017;64(7):e26421. doi:10.1002/pbc.26421
3. Salchow J, Mann J, Koch B, et al. Comprehensive assessments and related interventions to enhance the long-term outcomes of child, adolescent and young adult cancer survivors – presentation of the CARE for CAYA-Program study protocol and associated literature review. *BMC Cancer*. 2020;20(1):16. doi:10.1186/s12885-019-6492-5
4. Yanos PT, Ziedonis DM. The Patient-Oriented Clinician-Researcher: Advantages and Challenges of Being a Double Agent. *PS*. 2006;57(2):249-253. doi:10.1176/appi.ps.57.2.249
5. Koh WJ, Anderson BO, Carlson RW. NCCN Resource-Stratified and Harmonized Guidelines: A Paradigm for Optimizing Global Cancer Care. *Cancer*. 2020;126:2325-2493. doi:10.1002/cncr.32880,
6. Engert A, Younes A, eds. *Hodgkin Lymphoma: A Comprehensive Overview*. 3rd edition. Springer International Publishing; 2020. doi:10.1007/978-3-030-32482-7
7. Silva ROD, Ferreira JADOA, Rivera JA, Souza SSD, Nascimento-e-Silva D. Definition, elements and stages of elaboration of research protocols. *RSD*. 2020;9(10):e3189108721. doi:10.33448/rsd-v9i10.8721
8. What are clinical practice guidelines? In: *InformedHealth.Org [Internet]*. Institute for Quality and Efficiency in Health Care (IQWiG); 2016. Accessed September 9, 2023. <https://www.ncbi.nlm.nih.gov/books/NBK390308/>
9. Siegel DA, Richardson LC, Henley SJ, et al. Pediatric cancer mortality and survival in the United States, 2001-2016. *Cancer*. 2020;126(19):4379-4389. doi:10.1002/cncr.33080
10. Malpighi, Marcello. *De Viscerum Structura Exercitatio Anatomica. [Essay on the Anatomical Structure of the Viscera] (in Latin)*. Giacomo Monti.; 1666.
11. DeVita VT. A selective history of the therapy of Hodgkin's disease: Historical Review. *British Journal of Haematology*. 2003;122(5):718-727. doi:10.1046/j.1365-2141.2003.04541.x
12. Friedman DL, Chen L, Wolden S, et al. Dose-Intensive Response-Based Chemotherapy and Radiation Therapy for Children and Adolescents With Newly Diagnosed Intermediate-Risk Hodgkin Lymphoma: A Report From the Children's Oncology Group Study AHOD0031. *J Clin Oncol*. 2014;32(32):3651-3658. doi:10.1200/JCO.2013.52.5410
13. Dorff W, Claviez A, Albrecht M, et al. Treatment of children and adolescents with Hodgkin lymphoma without radiotherapy for patients in complete remission after chemotherapy: Final results of the multinational trial GPOH-HD95. *Journal of Clinical Oncology*. 2013;31(12):1562-1568. doi:10.1200/JCO.2012.45.3266
14. Bhethanabhotla S, Bakhshi S, Hematol A, Bhethanabhotla S, Bakhshi S. Presence of risk factors does not affect outcome in early stage pediatric Hodgkin lymphoma treated with ABVD. *Annals of Hematology*. 2017;96(3):521-522. doi:10.1007/s00277-016-2880-y

15. World Health Organization. *CureAll Framework: WHO Global Initiative for Childhood Cancer: Increasing Access, Advancing Quality, Saving Lives*. World Health Organization; 2021. Accessed August 12, 2022. <https://apps.who.int/iris/handle/10665/347370>
16. Henderson TO, Parsons SK, Wroblewski K, et al. Outcomes in Adolescents and Young Adults (AYA) with Hodgkin Lymphoma (HL) Treated on US Cooperative Group Protocols: An Adult Intergroup (E2496) and Children's Oncology Group (COG AHOD0031) Comparative Analysis. *Blood*. 2015;126(23):2636-2636. doi:10.1182/blood.V126.23.2636.2636
17. Tolu SS, Amengual JE. Queen's gambit: response-adapted win in CAYA with cHL. *Blood*. 2023;141(17):2037-2038. doi:10.1182/blood.2022019339
18. Mahajan A, Bakhshi S, Seth R, et al. Hodgkin Lymphoma in Children Under 5 Years: Do They Behave Differently? *J Pediatr Hematol Oncol*. 2022;44(4):186-190.
19. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. *CA A Cancer J Clinicians*. 2023;73(1):17-48. doi:10.3322/caac.21763
20. Stefan DC, Stones DK. The South African Paediatric Tumour registry - 25 years of activity. *South African Medical Journal*. 2012;102(7):605-606. doi:10.7196/SAMJ.6113
21. Abraham N. Childhood Cancer Registry 2019 Annual Report. *National Cancer Registry, South Africa* www.ncr.ac.za.
22. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood*. 2016;127(20):2375-2390. doi:10.1182/blood-2016-01-643569
23. Razack R, Michelow P, Leiman G, et al. An interinstitutional review of the value of FNAB in pediatric oncology in resource-limited countries. *Diagn Cytopathol*. 2012;40(9):770-776. doi:10.1002/dc.21624
24. Garg S, Rohilla M, Srinivasan R, et al. Fine-Needle Aspiration Diagnosis of Lymphoma Based on Cytomorphology Alone: How Accurate is it? - A Cyto-Histopathology Correlative Study. *J Cytol*. 2021;38(3):164-170. doi:10.4103/JOC.JOC_217_20
25. Weinstein HJ, Hudson MM, Link MP, eds. *Pediatric Lymphomas*. 1st edition. Springer International Publishing; 2007.
26. Toobaie A, Emil S, Ozgediz D, Krishnaswami S, Poenaru D. Pediatric surgical capacity in Africa: Current status and future needs. *Journal of Pediatric Surgery*. 2017;52(5):843-848. doi:10.1016/j.jpedsurg.2017.01.033
27. Kwoun W, Ahn J, Park P, et al. How useful is bone marrow study as an initial investigative tool without lymph node biopsy in malignant lymphoma?: Eleven years of experience at a single institution. *J Clin Lab Anal*. 2019;33(4):e22841. doi:10.1002/jcla.22841
28. Lister TA, Crowther D, Sutcliffe SB, et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. *Journal of Clinical Oncology*. 1989;7(11):1630-1636.
29. Rosenberg SA, Boiron M, DeVita VT, et al. Report of the Committee on Hodgkin's Disease Staging Procedures. *Cancer Research*. 1971;31(11):1862-1863.
30. Hagemeister FB, Fesus SM, Lamki LM, Haynie TP. Role of the gallium scan in Hodgkin's disease. *Cancer*. 1990;65(5):1090-1096.

31. Metzger ML, Hudson MM. Balancing Efficacy and Safety in the Treatment of Adolescents With Hodgkin's Lymphoma. *Journal of Clinical Oncology*. 2009;27(36):6071-6075.
32. Isasi CR, Lu P, Blaufox MD. A Metaanalysis of 18 F-2-Deoxy-2-Fluoro-D-Glucose Positron Emission Tomography in the Staging and Restaging of Patients with Lymphoma. *Cancer*. 2005;104(5):1066-1074. doi:10.1002/cncr.21253
33. Gallach M, Mikhail Lette M, Abdel-Wahab M, Giammarile F, Pellet O, Paez D. Addressing Global Inequities in Positron Emission Tomography-Computed Tomography (PET-CT) for Cancer Management: A Statistical Model to Guide Strategic Planning. *Med Sci Monit*. 2020;26. doi:10.12659/MSM.926544
34. Ellis GK, Chapman H, Manda A, et al. Pediatric lymphoma patients in Malawi present with poor health-related quality of life at diagnosis and improve throughout treatment and follow-up across all Pediatric PROMIS-25 domains. *Pediatric Blood & Cancer*. 2021;68(10). doi:10.1002/pbc.29257
35. Engel M. Improved prognosis of Epstein-Barr virus associated childhood Hodgkin's lymphoma: study of 47 South African cases. *Journal of Clinical Pathology*. 2000;53(3):182-186. doi:10.1136/jcp.53.3.182
36. Harif M, Madani A, Hessissen L, et al. Maladie de Hodgkin de l'enfant. Expérience marocaine. *Archives de Pédiatrie*. 2009;16(6):675-677. doi:10.1016/S0929-693X(09)74108-9
37. Hessissen L, Khtar R, Madani A, et al. Improving the Prognosis of Pediatric Hodgkin Lymphoma in Developing Countries: A Moroccan Society of Pediatric Hematology and Oncology Study. *Pediatric Blood and Cancer*. 2013;60:1464-1469. doi:10.1002/pbc.24534
38. El-Badawy S, Mokhless A. Risk Adapted Combined Modality Treatment in Children with Hodgkin's Disease: NCI, Cairo. *Journal of the Egyptian National Cancer Institute*. 2008;20(2):99-110.
39. Keller FG, Castellino SM, Chen L, et al. Results of the AHOD0431 trial of response adapted therapy and a salvage strategy for limited stage, classical Hodgkin lymphoma: A report from the Children's Oncology Group. *Cancer*. 2018;124(15):3210-3219. doi:10.1002/cncr.31519
40. Kelly KM, Cole PD, Pei Q, et al. Response-adapted therapy for the treatment of children with newly diagnosed high risk Hodgkin lymphoma (AHOD0831): a report from the Children's Oncology Group. *Br J Haematol*. 2019;187(1):39-48. doi:10.1111/bjh.16014
41. PDQ Pediatric Treatment Editorial Board. Childhood Hodgkin Lymphoma Treatment (PDQ®): Health Professional Version. In: *PDQ Cancer Information Summaries*. National Cancer Institute (US); 2002. Accessed November 19, 2023. <http://www.ncbi.nlm.nih.gov/books/NBK65726/>
42. Mauz-Körholz C, Landman-Parker J, Balwierz W, et al. Response-adapted omission of radiotherapy and comparison of consolidation chemotherapy in children and adolescents with intermediate-stage and advanced-stage classical Hodgkin lymphoma (EuroNet-PHL-C1): a titration study with an open-label, embedded, multinational, non-inferiority, randomised controlled trial. *The Lancet Oncology*. 2022;23(1):125-137. doi:10.1016/S1470-2045(21)00470-8
43. EuroNet-PHL-C2 | GPOH. Accessed November 19, 2023. https://www.gpoh.de/studienportal/abgeschlossene_studien_register/euroNet_phl_c2/index_ger.html
44. Jain S, Bakhshi S, Seth R, et al. Risk based and response adapted radiation therapy for children and adolescents with newly diagnosed advanced stage Hodgkin lymphoma treated with ABVD

- chemotherapy: a report from the Indian pediatric oncology group study InPOG-HL-15-01. *Leukemia & Lymphoma*. 2022;63(5):1111-1118. doi:10.1080/10428194.2021.2012659
45. Traore F, Diagne Akonde FB, Togo B, et al. Treatment of childhood Hodgkin lymphoma in sub-Saharan Africa: A report from the French-African Paediatric Oncology Group (GFAOP). *South African Journal of Child Health*. 14(3):155-160. doi:10.7196/sajch.2020.v14i3.1723
 46. Sherief LM, Elsafy UR, Abdelkhalek ER, et al. Hodgkin Lymphoma in Childhood: Clinicopathological features and therapy outcome at 2 Centers From a Developing Country. *Medicine*. 2015;94(15):e670. doi:10.1097/MD.0000000000000670
 47. Geel J, Hendricks M, Goga Y, et al. SACCSG HL-2018. Barriers and enablers of a harmonized treatment protocol for childhood and adolescent Hodgkin lymphoma in South Africa. *Pediatric Hematology and Oncology*. Published online January 20, 2023:1-14. doi:10.1080/08880018.2022.2162651
 48. Pusey WA. Cases of sarcoma and of Hodgkin's disease treated by exposures to X-rays. A preliminary report. *JAMA*. 1902;38:166-169.
 49. Witkowska M, Majchrzak A, Smolewski P. The Role of Radiotherapy in Hodgkin's Lymphoma: What Has Been Achieved during the Last 50 Years? *BioMed Research International*. 2015;2015:1-8. doi:10.1155/2015/485071
 50. Pack GT, Molander DW. The Surgical Treatment of Hodgkin's Disease. *Cancer Research*. 1966;26(6):1254-1263.
 51. Lacher MJ. Role of surgery in Hodgkin's disease. *NEJM*. 1963;286(6):289-292. doi:https://doi.org/10.1056/nejm196302072680605
 52. Hoppe RT. Evolution of the techniques of radiation therapy in the management of lymphoma. *Int J Clin Oncol*. 2013;18(3):359-363. doi:10.1007/s10147-013-0556-3
 53. Aznar DMC, Asteggiano R, Banfill K. Radiotherapy and its consequences: what the cardiologist should know. *e-Journal of Cardiology Practice*. 2021;19(20).
 54. Thomson AB, Wallace WHB. Treatment of paediatric Hodgkin's disease: a balance of risks. *European Journal of Cancer*. 2002;38(4):468-477. doi:doi: 10.1016/s0959-8049(01)00335-5
 55. Adams MJ, Lipsitz SR, Colan SD, et al. Cardiovascular Status in Long-Term Survivors of Hodgkin ' s Disease Treated With Chest Radiotherapy. *Journal of Clinical Onco*. 2018;22(15):3139-3148. doi:10.1200/JCO.2004.09.109
 56. Schellong G, Pötter R, Brämswig J, et al. High Cure Rates and Reduced Long-Term Toxicity in Pediatric Hodgkin's Disease: The German-Austrian Multicenter Trial DAL-HD-90. *JCO*. 1999;17(12):3736-3744. doi:10.1200/JCO.1999.17.12.3736
 57. Mauz-Körholz, Hasenclever D, Dörffel W, et al. Procarbazine-Free OEPA-COPDAC Chemotherapy in Boys and Standard OPPA-COPP in Girls Have Comparable Effectiveness in Pediatric Hodgkin's Lymphoma: The GPOH-HD-2002 Study. *Journal of Clinical Oncology*. 2010;28(23):1-7. doi:10.1200/JCO.2009.26.9381
 58. Mauz-Körholz C, Hasenclever D, Holzendorf V, et al. Feasibility of VECOPA, a dose-intensive chemotherapy regimen for children and adolescents with intermediate and advanced stage Hodgkin lymphoma: results of the GPOH-HD-2002/VECOPA pilot trial. *Leukemia & Lymphoma*. 2015;56(5):1308-1314. doi:10.3109/10428194.2014.961011

59. Goodman LS, Wintrobe MM, Dameshek W, Goodman MJ, Gilman A, McLennan MT. Nitrogen Mustard Therapy: Use of Methyl-Bis(Beta-Chloroethyl)amine Hydrochloride and Tris(Beta-Chloroethyl)amine Hydrochloride for Hodgkin's Disease, Lymphosarcoma, Leukemia and Certain Allied and Miscellaneous Disorders. *Journal of the American Medical Association*. 1946;132(3):126-132. doi:10.1001/jama.1946.02870380008004
60. Scott J. The effect of nitrogen mustard and maintenance chlorambucil in the treatment of advanced Hodgkin's disease. *Cancer Chemother Rep*. 1963;27:27-32.
61. Moxley J, De Vita V, Brace K, Frei E. Intensive combination chemotherapy and X-irradiation in Hodgkin's disease. *Cancer Research*. 1967;27(7):1258-1263. doi:doi: 10.1158/0008-5472.CAN-16-0470
62. DeVita VT, Serpick AA, Carbone PC. Combination Chemotherapy in the Treatment of Advanced Hodgkin's Disease. *Ann Intern Med*. 1970;73(6):881. doi:10.7326/0003-4819-73-6-881
63. Horning SJ, Rosenberg SA, Hoppe RT. Brief chemotherapy (Stanford V) and adjuvant radiotherapy for bulky or advanced Hodgkin's disease: An update. *Annals of Oncology*. 1996;7:S105-S108. doi:10.1093/annonc/7.suppl_4.S105
64. Longo DL, Duffey PL, DeVita VT, et al. Treatment of advanced-stage Hodgkin's disease: alternating noncrossresistant MOPP/CABS is not superior to MOPP. *JCO*. 1991;9(8):1409-1420. doi:10.1200/JCO.1991.9.8.1409
65. Straus DJ. Long-term survivorship at a price: late-term, therapy-associated toxicities in the adult Hodgkin lymphoma patient. *Therapeutic Advances in Hematology*. 2011;2(2):111-119. doi:10.1177/2040620711402414
66. Fisher RI. Prolonged Disease-Free Survival in Hodgkin's Disease with MOPP Reinduction After First Relapse. *Ann Intern Med*. 1979;90(5):761. doi:10.7326/0003-4819-90-5-761
67. Moore MR, Jones SE, Bull JM, William LA, Rosenberg SA. MOPP chemotherapy for advanced Hodgkin's disease. Prognostic factors in 81 patients. *Cancer*. 1973;32(1):52-60. doi:10.1002/1097-0142(197307)32:1<52::AID-CNCR2820320107>3.0.CO;2-S
68. Bonadonna G, Zucali R, Monfardini S, de Lena M, Uslenghi C. Combination chemotherapy of Hodgkin's disease with adriamycin, bleomycin, vinblastine, and imidazole carboxamide versus MOPP. *Cancer*. 1975;36:252-259. doi:10.1002/1097-0142(197507)36:1<252::AID-CNCR2820360128>3.0.CO;2-7
69. Mittal A, Bhethanabhotla S, Ganguly S, et al. Late effects in pediatric Hodgkin lymphoma survivors after uniform treatment with ABVD with or without radiotherapy. *Pediatr Blood Cancer*. 2021;68(11). doi:10.1002/pbc.29293
70. Weiner MA, Leventhal BG, Marcus R, et al. Intensive chemotherapy and low-dose radiotherapy for the treatment of advanced-stage Hodgkin's disease in pediatric patients: a Pediatric Oncology Group study. *JCO*. 1991;9(9):1591-1598. doi:10.1200/JCO.1991.9.9.1591
71. Shankar A, Visaduraki M, Hayward J, Morland B, McCarthy K, Hewitt M. Clinical outcome in children and adolescents with Hodgkin lymphoma after treatment with chemotherapy alone – The results of the United Kingdom HD3 national cohort trial. *European Journal of Cancer*. 2012;48(1):108-113. doi:10.1016/j.ejca.2011.05.029
72. Mauz-Körholz C, Metzger ML, Kelly KM, et al. Pediatric Hodgkin Lymphoma. *JCO*. 2015;33(27):2975-2985. doi:10.1200/JCO.2014.59.4853

73. Schellong G. The balance between cure and late effects in childhood Hodgkin's lymphoma: The experience of the German-Austrian Study-Group since 1978. *Annals of Oncology*. 1996;7:S67-S72. doi:10.1093/annonc/7.suppl_4.S67
74. Schellong G, Brämwig J, Ludwig R, et al. Kombinierte Behandlungsstrategie bei über 200 Kindern mit Morbus Hodgkin: Abgestufte Chemotherapie, Involved-Field-Bestrahlung mit erniedrigten Dosen und selektive Splenektomie. Ein Bericht der kooperativen Therapiestudie DAL-HD-82. *Klin Padiatr*. 1986;198(03):137-146. doi:10.1055/s-2008-1026870
75. Castellanos EM, Barrantes JC, Báez LF, et al. A chemotherapy only therapeutic approach to pediatric Hodgkin lymphoma: AHOPCA LH 1999: Treatment of Hodgkin Lymphoma in AHOPCA. *Pediatr Blood Cancer*. 2014;61(6):997-1002. doi:10.1002/pbc.24905
76. Castellino SM, Pei Q, Parsons SK, et al. Brentuximab Vedotin with Chemotherapy in Pediatric High-Risk Hodgkin's Lymphoma. *N Engl J Med*. 2022;387(18):1649-1660. doi:10.1056/NEJMoa2206660
77. Algeri M, Locatelli F. Pembrolizumab (and friends) in pediatric malignancies: should we consider Hodgkin lymphoma a world of its own? *Ann Transl Med*. 2020;8(17):1112-1112. doi:10.21037/atm.2020.04.54
78. Kozlov AV, Kazantzev IV, Iukhta TV, et al. Nivolumab in pediatric Hodgkin's lymphoma. *CTT*. 2019;8(4):41-48. doi:10.18620/ctt-1866-8836-2019-8-4-41-48
79. National Essential Medicines List Committee (NEMLC) Tertiary and quaternary level essential medicines list. Reviewed Items June 2022. Published online June 2022. https://knowledgehub.health.gov.za/system/files/elibdownloads/2023-02/Tertiary%20and%20Quaternary%20Level%20Essential%20Medicine%20Recommendations_June%202022.pdf
80. Cheson BD, Horning SJ, Coiffier B, et al. Report of an International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphomas. *Journal of Clinical Oncology*. 1999;17(4):1244-1253.
81. Cheson BD, Pfistner B, Juweid ME, et al. Revised Response Criteria for Malignant Lymphoma. *JCO*. 2007;25(5):579-586. doi:10.1200/JCO.2006.09.2403
82. Cheson BD. Staging and response assessment in lymphomas: the new Lugano classification. *Chin Clin Oncol*. 2015;4(1):1-9. doi:10.3978/j.issn.2304-3865.2014.11.03
83. De Re V, Caggiari L, Repetto O, Mussolin L, Mascarin M. Classical Hodgkin's Lymphoma in the Era of Immune Checkpoint Inhibition. *JCM*. 2019;8(10):1596. doi:10.3390/jcm8101596
84. Mechita NB, Cherkaoui S, Abousselham L, et al. Implementing the WHO Global Initiative for Childhood Cancer in Morocco: Survival study for the six indexed childhood cancers. *Pediatric Blood & Cancer*. 2022;69(10). doi:10.1002/pbc.29788
85. Soliman RM, Elhaddad A, Oke J, et al. Temporal trends in childhood cancer survival in Egypt, 2007 to 2017: A large retrospective study of 14 808 children with cancer from the Children's Cancer Hospital Egypt. *International Journal of Cancer*. 2020;(April):1-13. doi:10.1002/ijc.33321
86. Hesseling PB, Wessels G, Van Jaarsveld D, Van Riet F. Hodgkin disease in children in Southern Africa: epidemiological characteristics, morbidity and long-term outcome. *Annals of Tropical Paediatrics*. 1997;17:367-373.

87. Padayachee RS, Perner Y, MacKinnon D, Rowe B, Pather S. A retrospective analysis of paediatric lymphomas at Chris Hani Baragwanath Academic Hospital in Soweto, South Africa. *Annals of Diagnostic Pathology*. 2018;33:51-57. doi:10.1016/j.anndiagpath.2017.11.006
88. Jacobson RJ, Klappenbach RS, Clinton C, De Moor NG, Wong O. Hodgkin's disease in South African children. *South African Medical Journal*. 1981;59(133).
89. Jacobs P, King HS, Karabus C, Hartley P, Werner D. Hodgkin's disease in children. A ten-year experience in South Africa. *Cancer*. 1984;53(2):210-213. doi:10.1002/1097-0142(19840115)53:2<210::AID-CNCR2820530204>3.0.CO;2-Z
90. Geneva. Joint United Nations Programme on HIV/AIDS. *UNAIDS Data 2022*; 2022. <https://creativecommons.org/licenses/by-nc-sa/3.0/igo/>
91. Payne S, Seymour J, Molassiotis A, et al. Benefits and challenges of collaborative research: lessons from supportive and palliative care. *BMJ Supportive & Palliative Care*. 2011;1(1):5-11. doi:10.1136/bmjspcare-2011-000018
92. Parascandola M, Pearlman PC, Eldridge L, Gopal S. The Development of Global Cancer Research at the United States National Cancer Institute. *JNCI: Journal of the National Cancer Institute*. 2022;114(9):1228-1237. doi:10.1093/jnci/djac104
93. Gagliardi AR, Dobrow MJ, Wright FC. How can we improve cancer care? A review of interprofessional collaboration models and their use in clinical management. *Surgical Oncology*. 2011;20(3):146-154. doi:10.1016/j.suronc.2011.06.004
94. Vaishnavi K, Bansal D, Trehan A, Jain R, Attri SV. Improving the safety of high-dose methotrexate for children with hematologic cancers in settings without access to MTX levels using extended hydration and additional leucovorin. *Pediatr Blood Cancer*. 2018;65(12):e27241. doi:10.1002/pbc.27241
95. Hesselting P, Broadhead R, Mansvelt E, et al. The 2000 Burkitt lymphoma trial in Malawi. *Pediatr Blood Cancer*. 2005;44(3):245-250. doi:10.1002/pbc.20254
96. Harif M, Barsaoui S, Bencheikroun S, et al. Treatment of B-cell lymphoma with LMB modified protocols in Africa—report of the French-African Pediatric Oncology Group (GFAOP). *Pediatr Blood Cancer*. 2008;50(6):1138-1142. doi:10.1002/pbc.21452
97. Stones DK, De Bruin GP, Esterhuizen T, Stefan DC. Childhood cancer survival rates in two South African units. *South African Medical Journal*. 2014;104(7):502-504.
98. Beringer N, Bennett KG, Poole JE, Geel JA. Determinants of survival in children with cancer in Johannesburg, South Africa. *South African Journal of Oncology*. 2021;5. doi:10.4102/sajo.v5i0.189
99. Bleyer WA. The U.S. pediatric cancer clinical trials programmes: International implications and the way forward. *European Journal of Cancer*. 1997;33(9):1439-1447. doi:10.1016/S0959-8049(97)00249-9
100. Ozuah NW, Marcus KJ, LaCasce AS, Billett AL. Excellent Outcomes Following Response-based Omission of Radiotherapy in Children and Adolescents With Intermediate or High-risk Hodgkin Lymphoma. *Journal of Pediatric Hematology/Oncology*. 2018;40(6):e338-e342. doi:10.1097/MPH.0000000000001076
101. Ngoya PS, Muhogora WE, Pitcher RD. Defining the diagnostic divide: an analysis of registered radiological equipment resources in a low-income African country. *Pan Afr Med J*. 2016;25. doi:10.11604/pamj.2016.25.99.9736

102. Grover S, Xu MJ, Yeager A, et al. A Systematic Review of Radiotherapy Capacity in Low- and Middle-Income Countries. *Front Oncol*. 2015;4. doi:10.3389/fonc.2014.00380
103. Fervers B, Burgers JS, Haugh MC, et al. Adaptation of clinical guidelines: literature review and proposition for a framework and procedure. *International Journal for Quality in Health Care*. 2006;18(3):167-176. doi:10.1093/intqhc/mzi108
104. Davidson A, Wainwright RD, Stones DK, et al. Malignancies in South African children with HIV. *Journal of Pediatric Hematology/Oncology*. 2014;36(2):111-117. doi:10.1097/MPH.0b013e31829cdd49
105. Kelly KM, Sposto R, Hutchinson R, et al. BEACOPP chemotherapy is a highly effective regimen in children and adolescents with high-risk Hodgkin lymphoma: a report from the Children's Oncology Group. *Blood*. 2011;117(9):2596-2603. doi:10.1182/blood-2010
106. Schwartz CL, Constine LS, Villaluna D, et al. A risk-adapted, response-based approach using ABVE-PC for children and adolescents with intermediate- and high-risk Hodgkin lymphoma: The results of P9425. *Blood*. 2009;114(10):2051-2059. doi:10.1182/blood-2008-10-184143
107. Jain S, Kapoor G, Bajpai R. ABVD-Based Therapy for Hodgkin Lymphoma in Children and Adolescents: Lessons Learnt in a Tertiary Care Oncology Center in a Developing Country. *Pediatric Blood and Cancer*. 2016;63:1024-1030. doi:10.1002/pbc.25935
108. Oberlin O, Patte C. Treatment of Newly Diagnosed and Relapsed Hodgkin Lymphoma in Children. *Iranian Journal of Blood and Cancer*. 2015;7(5):206-212.
109. Flerlage JE, Hiniker SM, Armenian S, et al. Pediatric Hodgkin Lymphoma, Version 3.2021. *Journal of the National Comprehensive Cancer Network*. 2021;19(6):733-754. doi:10.6004/jnccn.2021.0027
110. Zubizarreta PA, Alfaro E, Gutter M, et al. Children and Adolescent Hodgkin Lymphoma in Argentina: Long-term Results After Combined ABVD and Restricted Radiotherapy. *Journal of Pediatric Hematology/Oncology*. 2017;39(8):602-608. doi:10.1097/MPH.0000000000000943
111. Mondello P, Musolino C, Dogliotti I, et al. ABVD vs BEACOPP escalated in advanced-stage Hodgkin's lymphoma: Results from a multicenter European study. *American J Hematol*. 2020;95(9):1030-1037. doi:10.1002/ajh.25871
112. Grobbelaar S, Mercier AE, Verburgh E, Brittain D, Pepper MS. Haematopoietic stem cell transplantation in South Africa: Current limitations and future perspectives. *S Afr Med J*. 2019;109(8b):46. doi:10.7196/SAMJ.2019.v109i8b.013888
113. Santoro A, Bonadonna G, Valagussa P, et al. Long-term results of combined chemotherapy-radiotherapy approach in Hodgkin's disease: superiority of ABVD plus radiotherapy versus MOPP plus radiotherapy. *JCO*. 1987;5(1):27-37. doi:10.1200/JCO.1987.5.1.27
114. Stieglitz E, Dinh T, Phelps AS, Pampaloni MH, Olshen AB, Robbins E. ABVD Without Radiation for Newly Diagnosed Pediatric and Young Adult Patients With Hodgkin Lymphoma: A Single Center Retrospective Analysis of 28 Consecutive Patients. *Journal of Pediatric Hematology/Oncology*. 2018;40(4):290-294. doi:10.1097/MPH.0000000000001094
115. Pavlovsky S, Corrado C, Pavlovsky MA, et al. Risk-Adapted Therapy With Three or Six Cycles of Doxorubicin/Bleomycin/Vinblastine/Dacarbazine Plus Involved-Field Radiation Therapy in Hodgkin Lymphoma, Based on Prognosis at Diagnosis and Early Response: Results From the GATLA Study. *Clinical Lymphoma Myeloma and Leukemia*. 2010;10(3):181-185. doi:10.3816/CLML.2010.n.028

116. Jaime-Pérez JC, Gamboa-Alonso CM, Padilla-Medina JR, et al. High frequency of primary refractory disease and low progression-free survival rate of Hodgkin's lymphoma: a decade of experience in a Latin American center. *Revista Brasileira de Hematologia e Hemoterapia*. 2017;39(4):325-330. doi:10.1016/j.bjhh.2017.08.001
117. Hajian-Tilaki K. Receiver Operating Characteristic (ROC) Curve Analysis for Medical Diagnostic Test Evaluation. *Caspian Journal of Internal Medicine*. 2013;4(2):627-635.
118. Talari K, Goyal M. Retrospective Studies – Utility and Caveats. *Journal of the Royal College of Physicians of Edinburgh*. 2020;50(4):398-402. doi:10.4997/jrcpe.2020.409
119. Fabian ID, Stacey AW, Foster A, et al. Travel burden and clinical presentation of retinoblastoma: analysis of 1024 patients from 43 African countries and 518 patients from 40 European countries. *Br J Ophthalmol*. 2021;105(10):1435-1443. doi:10.1136/bjophthalmol-2020-316613
120. Fabian ID, Abdallah E, Abdullahi SU, et al. The Global Retinoblastoma Outcome Study: a prospective, cluster-based analysis of 4064 patients from 149 countries. *The Lancet Global Health*. 2022;10(8):e1128-e1140. doi:10.1016/S2214-109X(22)00250-9
121. Global Retinoblastoma Study Group, Fabian ID, Abdallah E, et al. Global Retinoblastoma Presentation and Analysis by National Income Level. *JAMA Oncol*. 2020;6(5):685. doi:10.1001/jamaoncol.2019.6716
122. Ghafoor T. Prognostic factors in pediatric Hodgkin lymphoma: experience from a developing country. *Leukemia & Lymphoma*. 2020;61(2):344-350. doi:10.1080/10428194.2019.1665666
123. Ladas EJ, Arora B, Howard SC, Rogers PC, Mosby TT, Barr RD. A Framework for Adapted Nutritional Therapy for Children With Cancer in Low- and Middle-Income Countries: A Report From the SIOP PODC Nutrition Working Group: A Framework for Nutritional Care in LMIC. *Pediatr Blood Cancer*. 2016;63(8):1339-1348. doi:10.1002/pbc.26016
124. Bhethanabhotla S, Jain S, Kapoor G, et al. Outcome of pediatric advanced Hodgkin lymphoma treated with ABVD and predictors of inferior survival: a multicenter study of 186 patients. *Leukemia & Lymphoma*. 2017;58(7):1617-1623. doi:10.1080/10428194.2016.1262951
125. Nattrass N. South Africa's "Rollout" of Highly Active Antiretroviral Therapy: A Critical Assessment. *JAIDS Journal of Acquired Immune Deficiency Syndromes*. 2006;43(5):618-623. doi:10.1097/01.qai.0000242456.05274.fb
126. HIV/AIDS Infections / Countries of the World. Accessed July 16, 2023. <https://www.citypopulation.de/en/world/bymap/hivinfections/>
127. DeBoer RJ, Shyirambere C, Driscoll CD, et al. Treatment of Hodgkin Lymphoma With ABVD Chemotherapy in Rural Rwanda: A Model for Cancer Care Delivery Implementation. *JCO Global Oncology*. 2020;(6):1093-1102. doi:10.1200/GO.20.00088
128. Gini Coefficient by Country 2023. Accessed July 16, 2023. <https://worldpopulationreview.com/country-rankings/gini-coefficient-by-country>
129. Benatar S, Gill S. Universal Access to Healthcare: The Case of South Africa in the Comparative Global Context of the Late Anthropocene Era. *Int J Health Policy Manag*. Published online March 1, 2020;1. doi:10.34172/ijhpm.2020.28
130. University of Rochester Medical Center. www.urmc.rochester.edu. Published November 27, 2023.

131. Kaspers GJL. COVID-19: how will this impact children with cancer, now and in the future? *Expert Review of Anticancer Therapy*. 2020;20(7):527-529. doi:10.1080/14737140.2020.1781621
132. Kutluk MT, Ahmed F, Kirazlı M, et al. The effect of the COVID-19 pandemic on paediatric cancer care: lessons learnt from a major paediatric oncology department in Turkey. *ecancer*. 2021;15:1172. doi:https://doi.org/10.3332/ecancer.2021.1172
133. Arora RS, Mahajan A, Dinand V, et al. InPOG-HL-15-01 - Challenges and lessons learnt in setting up the first collaborative multicentre prospective clinical trial in childhood cancer in India. *Pediatric Hematology Oncology Journal*. 2020;5(4):166-170. doi:10.1016/j.phoj.2020.02.001
134. Hasenclever D. The disappearance of prognostic factors in Hodgkin's disease. *Annals of Oncology*. 2002;13(1):75-78. doi:10.1093/annonc/mdf615
135. Committee on Standards for Developing Trustworthy Clinical Practice Guidelines, Board on Health Care Services, Institute of Medicine. *Clinical Practice Guidelines We Can Trust*. (Graham R, Mancher M, Wolman DM, Greenfield S, Steinberg E, eds.). National Academies Press; 2011:13058. doi:10.17226/13058
136. Camlin CS, Charlebois ED, Getahun M, et al. Pathways for reduction of HIV-related stigma: a model derived from longitudinal qualitative research in Kenya and Uganda. *J Intern AIDS Soc*. 2020;23(12):e25647. doi:10.1002/jia2.25647
137. Peppercorn JM, Weeks JC, Cook EF, Joffe S. Comparison of outcomes in cancer patients treated within and outside clinical trials: conceptual framework and structured review. *The Lancet*. 2004;363(9405):263-270. doi:10.1016/S0140-6736(03)15383-4
138. Wallace WHB, Thomson AB, Saran F, Kelsey TW. Predicting age of ovarian failure after radiation to a field that includes the ovaries. *International Journal of Radiation Oncology*. 2005;62(3):738-744. doi:10.1016/j.ijrobp.2004.11.038
139. Cleaton-Jones P. Scientific misconduct in a breast-cancer chemotherapy trial: response of University of the Witwatersrand. *The Lancet*. 2000;355(9208):1011-1012. doi:10.1016/S0140-6736(00)90003-5
140. Weyzig F, Schipper I. SOMO briefing paper on ethics in clinical trials: Examples of unethical trials. Published online February 2008. <https://www.somo.nl/examples-of-unethical-trials/>
141. Saginur R, Dent SF, Schwartz L, Heslegrave R, Stacey S, Manzo J. Ontario cancer research ethics board: Lessons learned from developing a multicenter regional institutional review board. *Journal of Clinical Oncology*. 2008;26(9):1479-1482. doi:10.1200/JCO.2007.12.6441
142. Chaddah MR. The Ontario Cancer Research Ethics Board: A Central REB That Works. *Current Oncology*. 2008;15(1):49-52. doi:10.3747/co.2008.196
143. Van Heerden J, Zaghloul M, Neven A, et al. JCO Global Oncology Pediatric oncology clinical trials and collaborative research in Africa : current landscape and future perspectives. *Journal of Global Oncology*. 2020;6:1264-1275.
144. NCCN News. *Journal of the National Comprehensive Cancer Network*. 2023;21(2):xiv-xvii. doi:10.6004/jnccn.2023.0010
145. Population of Africa (2023) - Worldometer. Accessed August 17, 2023. <https://www.worldometers.info/world-population/africa-population/>

146. ARIA Guide. St. Jude Global Alliance. Accessed July 15, 2023. <https://stg-global.stjude.org/en-us/tools/sj-cares-tools/aria-guide.html>
147. Belgaumi AF, Anas M, Siddiqui KS, Akhter MF, Al-Kofide A. Risk-adapted stratification for optimally intensive treatment assignment of pediatric patients with non-Hodgkin lymphoma is an effective strategy in developing countries. *Pediatr Blood Cancer*. 2017;64(6):e26335. doi:10.1002/pbc.26335
148. Moleti ML, Al-Jadiry MF, Shateh WA, et al. Long-term results with the adapted LMB 96 protocol in children with B-cell non-Hodgkin lymphoma treated in Iraq: comparison in two subsequent cohorts of patients. *Leukemia & Lymphoma*. 2019;60(5):1224-1233. doi:10.1080/10428194.2018.1519810
149. ICMJE | Recommendations | Defining the Role of Authors and Contributors. Accessed November 20, 2023. <https://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html>
150. Mariani AW, Pego-Fernandes PM. Observational studies: why are they so important? *Sao Paulo Med J*. 2014;132(1):01-02. doi:10.1590/1516-3180.2014.1321784