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Clinical presentation and diagnosis of adult patients with non-Hodgkin lymphoma in Sub-Saharan Africa

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Summary

Non-Hodgkin lymphoma (NHL) is the sixth most common cancer in Sub-Saharan Africa (SSA). Comprehensive diagnostics of NHL are essential for effective treatment. Our objective was to assess the frequency of NHL subtypes, disease stage and further diagnostic aspects. Eleven population-based cancer registries in 10 countries participated in our observational study. A random sample of 516 patients was included. Histological confirmation of NHL was available for 76.2% and cytological confirmation for another 17.3%. NHL subclassification was determined in 42.1%. Of these, diffuse large B cell lymphoma, chronic lymphocytic leukaemia and Burkitt lymphoma were the most common subtypes identified (48.8%, 18.4% and 6.0%, respectively). We traced 293 patients, for whom recorded data were amended using clinical records. For these, information on stage, human immunodeficiency virus (HIV) status and Eastern Cooperative Oncology Group Performance Status (ECOG PS) was available for 60.8%, 52.6% and 45.1%, respectively. Stage at diagnosis was advanced for 130 of 178 (73.0%) patients, HIV status was positive for 97 of 154 (63.0%) and ECOG PS was ≥2 for 81 of 132 (61.4%). Knowledge about NHL subclassification and baseline clinical characteristics is crucial for guideline-recommended treatment. Hence, regionally adapted investments in pathological capacity, as well as standardised clinical diagnostics, will significantly improve the therapeutic precision for NHL in SSA.

Keywords: non-Hodgkin lymphoma, Sub-Saharan Africa, regional distribution, diagnostics, human immunodeficiency virus, public health.

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Introduction

Non-Hodgkin lymphoma (NHL) is the sixth most common type of malignant neoplasia in Sub-Saharan Africa (SSA), with incidence continuously rising and burden expected to double by 2040 (Parkin *et al.*, 2010; Chokunonga *et al.*, 2013; Bray *et al.*, 2018). NHL is a heterogeneous disease, with >80 subtypes identified (Swerdlow *et al.*, 2016). In SSA, infectious agents are important causes of lymphoma. A recent study reported that ~19.7% of NHL cases in SSA are attributable to infectious agents, with 12.7% of the cases related to human immunodeficiency virus (HIV) alone (Parkin *et al.*, 2019).

Non-Hodgkin lymphoma is aetiologically associated with Epstein–Barr virus (EBV) (Vockerodt *et al.*, 2015), human gammaherpesvirus 8 (Cesarman *et al.*, 1995), *helicobacter pylori* (Zucca *et al.*, 2014), human T-lymphotrophic virus 1 (Cook *et al.*, 2017), and malaria (Thorley-Lawson *et al.*, 2016), and epidemiologically associated with HIV (Grulich *et al.*, 2007; Shiels & Engels, 2012; Carbone *et al.*, 2014; Schonfeld *et al.*, 2016), even when controlled by antiretrovirals (Cesarman, 2013), and hepatitis C virus (Morton *et al.*, 2014; Miranda-Filho *et al.*, 2019). Other environmental, demographic, ethnic and lifestyle factors are likely to play an important role as well (Morton *et al.*, 2014). Identification of NHL subtype is crucial for specific therapy (Naresh *et al.*, 2011; Gopal *et al.*, 2012). In SSA, resources for diagnostic services and cancer care are limited, resulting in a high frequency of unclassified lymphoma and in poor clinical outcome (Gopal *et al.*, 2012; Mwamba *et al.*, 2012; Gopal *et al.*, 2016; Perry *et al.*, 2016b; Milligan *et al.*, 2018). The National Comprehensive Cancer Network (NCCN) developed resource-stratified guidelines on B cell lymphoma (Zelenetz *et al.*, 2019).

To date, data on quality of diagnostics have been published on hospital series only (e.g. Bateganya *et al.*, 2011; Naresh *et al.*, 2011; Wiggill *et al.*, 2011; Gopal *et al.*, 2016; Milligan *et al.*, 2018; Painschab *et al.*, 2019). The aim of the present study was to assess NHL subtype distribution and diagnostic services in a population-based cohort by collaborating with the African Cancer Registry Network (AFCRN). Data from registries in 10 countries were accessed for a retrospective analysis. Hence, the present study will help to provide a more complete picture of lymphoma diagnostics in SSA and contribute to improved diagnostic accuracy and patient management.

Patients and methods

Eleven population-based cancer registries (PBCRs) in 10 countries were selected as study centres, covering a population of ~21.5 million (Fig 1) (Parkin & Liu, 2019). These registries co-operate with oncological facilities, including hospitals and medical practices, in their respective registry areas from both the public and the private sector, and register all patients diagnosed with cancer in databases.

We included patients with NHL aged 15–99 years with International Classification of Diseases (ICD)-10 codes C82-C86 and C96 (April *et al.*, 2013) (Table S1) diagnosed between 2012 and 2013, extending the time period for some

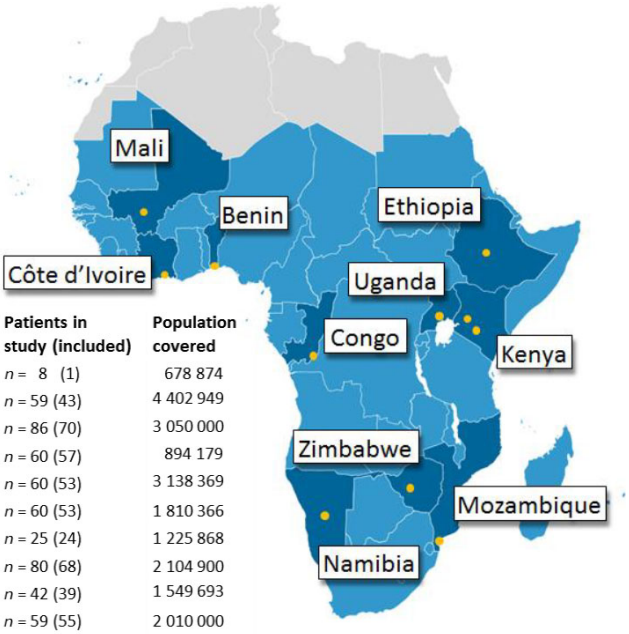
registries due to lack of patients. In total, 1068 patients were available in the registry databases. We assessed prevalence of adequate care from medical records among a random sample that could be assessed within feasible time and efforts in the given setting. We intended to draw conclusions for an SSA cohort, but not for individual registries. Therefore, no power was calculated for individual registries. A minimal sample size of 404 patients produces a two-sided 95% confidence interval with a width equal to 0.1 when the sample proportion of patients with adequate care is 0.500, which is the most conservative assumption. We assumed a drop-out rate of 33% and therefore aimed for 600 patients as our random sample. Thus, of 1068 patients available in registries, 599 patients (56.1%) were selected at random. In Brazzaville, Cotonou and Mozambique, all patients registered were included due to limited number of registered patients (Table I and Fig 2).

The AFCRN registry staff continuously retrieves information from hospital records and pathology reports (Am Finesse *et al.*, 2019). Data on sex and age, diagnosis and diagnostic modality are collected and coded according to current International Classification of Diseases for Oncology (ICD-O) standards (April *et al.*, 2013). To update the PBCR routine data, clinical records were re-evaluated. We considered registry data to be correct, unless the medical record gave differing information. Morphology was assessed from pathology reports, and, in the absence of definitive pathological diagnoses, those noted in clinical records were used.

A total of 41 diagnoses were reported according to Working Formulation classification (Rosenberg, 1982). For summary purposes, 11 diagnoses of '(diffuse) small cell NHL' were converted to 'low-grade NHL, unknown cellular lineage, not otherwise specified (NOS)' (ICD-O code 9591); and 23 diagnoses of '(diffuse) large cell NHL' were converted to 'high-grade NHL, unknown cellular lineage, NOS' (ICD-O code 9591). The remaining seven Working Formulation diagnoses were defined as NHL, NOS (unclassified NHL, ICD-O code 9591). Eight other patients pathologically diagnosed as low-grade NHL (three) and high-grade NHL (five) without any further classification were assigned to ICD-O code 9591, low-grade and high-grade, respectively. The diagnostic modality provided by registries, that is, histology, cytology, or clinical diagnosis without any specimen analysis, was amended if additional information on fine needle aspiration cytology (FNAC) or histological confirmation was found.

Furthermore, we traced data not available in PBCR databases: B symptoms, Eastern Cooperative Oncology Group Performance Status (ECOG PS), stage, HIV status and information on imaging. Stage was assessed in line with Lugano and Binet classification (Cheson *et al.*, 2014; Hallek, 2017). When stage had not been assigned in records, it was considered less advanced if no suggestion of disseminated nodal or extranodal involvement was found. When uncertain about primary or secondary extranodal lymphoma in advanced stages, we considered disease to be primary nodal rather than primary extranodal. Patients were considered to have 'traced clinical information' if information beyond the basic PBCR data was obtained from hospital and pathology records: Stage, B symptoms, ECOG PS, HIV status and imaging. For patients not traced, no information beyond the basic PBCR data was available.

For further analysis, patients were allocated to six groups: subclassified high-grade B cell NHL, subclassified low-grade B cell NHL, subclassified T cell NHL, otherwise subclassified



Population-based cancer registry	Patients in study (included)	Population covered
Benin – Cotonou	*n* = 8 (1)	678 874
Côte d'Ivoire – Abidjan	*n* = 59 (43)	4 402 949
Ethiopia – Addis Ababa	*n* = 86 (70)	3 050 000
Kenya – Eldoret	*n* = 60 (57)	894 179
Kenya – Nairobi	*n* = 60 (53)	3 138 369
Mali – Bamako	*n* = 60 (53)	1 810 366
Mozambique – Maputo	*n* = 25 (24)	1 225 868
Namibia – nation-wide	*n* = 80 (68)	2 104 900
Congo – Brazzaville	*n* = 42 (39)	1 549 693
Uganda – Kampala	*n* = 59 (55)	2 010 000
Zimbabwe – Bulawayo	*n* = 60 (53)	653 000

Fig. 1. Map of Sub-Saharan Africa (Wikimedia Commons, 2019). Countries and cities of participating population-based cancer registries are highlighted; together with number of patients in random sample drawn, number of patients included in the study and population covered in each registry area. [Colour figure can be viewed at wileyonlinelibrary.com]

Table I. Population-based cancer registries (PBCR) and study population characteristics.

PBCR (years observed)	Patients registered in PBCR during years observed, *n*	Population-based sample, *n* (% of patients registered in PBCRs during years observed)	Patients excluded, *n* (% of population-based sample)	Total cohort, *n*	Patients traced, *n* (% of total cohort)
Abidjan (2012–2013)	112	59 (52.7)	16 (27.1)	43	30 (69.8)
Addis Ababa (2012 and 2014)	103	86 (83.5)	16 (18.6)	70	33 (47.1)
Bamako (2012–2013)	61	60 (98.4)	7 (11.7)	53	20 (37.8)
Brazzaville (2011–2014)	42	42 (100)	3 (7.1)	39	6 (15.4)
Bulawayo (2012–2013)	198	60 (30.3)	7 (11.7)	53	36 (67.9)
Cotonou (2013–2014)	8	8 (100)	7 (87.5)	1	1 (100)
Eldoret (2012–2013)	68	60 (88.2)	3 (5.0)	57	21 (36.8)
Kampala (2012–2013)	94	59 (62.8)	4 (6.8)	55	40 (72.7)
Maputo (2014–2015)	25	25 (100)	1 (4.0)	24	17 (70.8)
Nairobi (2012–2013)	196	60 (30.6)	7 (11.7)	53	44 (83.0)
Namibia (2012–2013)	161	80 (49.7)	12 (15.0)	68	45 (66.2)
11 PBCRs (2011–2015)	1.068	599 (56.1)	83 (13.9)	516	293 (56.8)

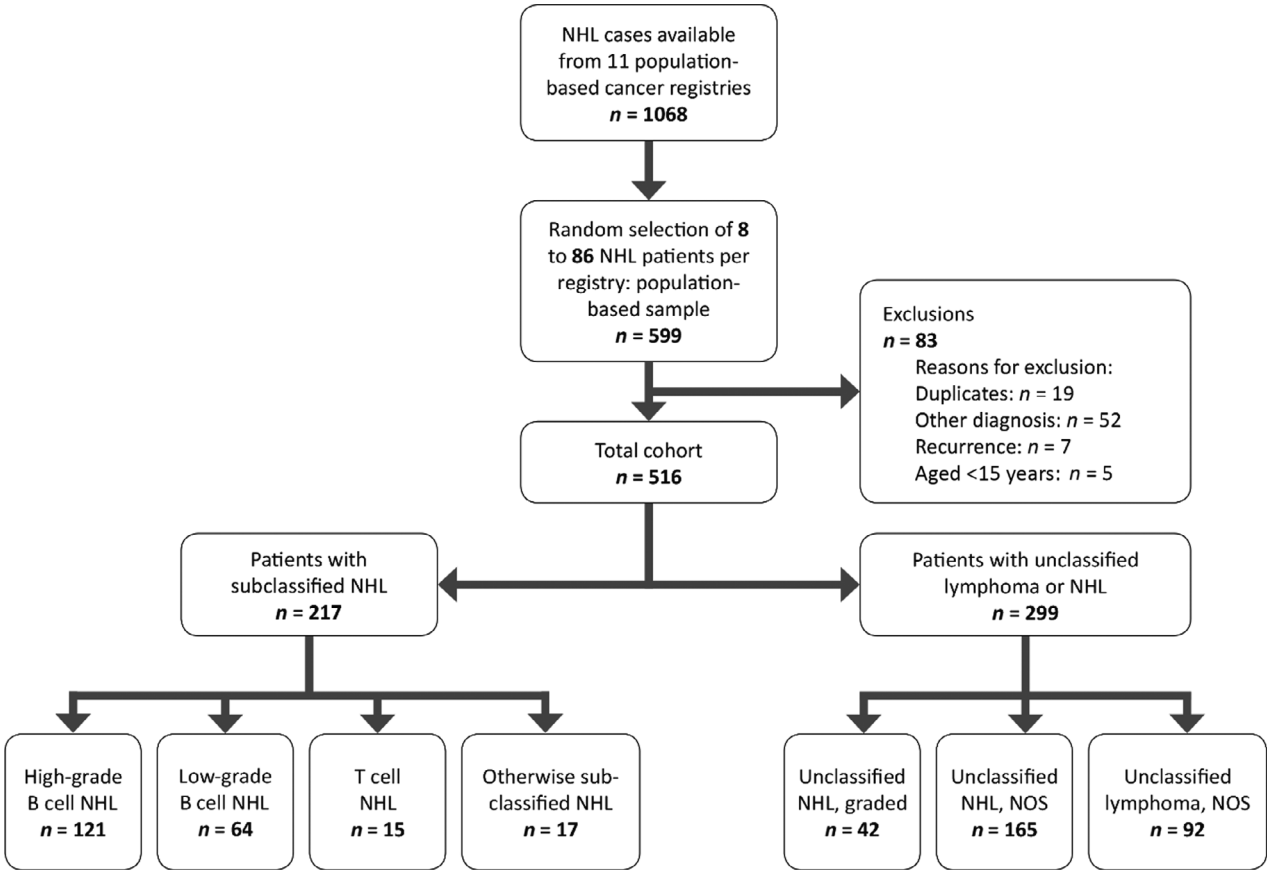


Fig. 2. Flowchart of study population. Stratified by non-Hodgkin lymphoma groups. NHL, non-Hodgkin lymphoma; NOS, not otherwise specified.

NHL, unclassified and graded NHL, and unclassified NHL or lymphoma, not graded (Table II).

According to NCCN guidelines harmonised for SSA (Zelenetz *et al.*, 2019), we established an evaluation scheme for quality of pathological diagnosis and completeness of clinical diagnostic criteria. We revised availability of NHL subclassification, information on grade for unclassified NHL and diagnostic modality. We were unable to evaluate

Table II. Proportions of morphological subtypes within the non-Hodgkin lymphoma groups.

Lymphoma classification	ICD-O morphology codes	Patients, *n* (%)
All subclassified NHL		**217 (42.1)**†
Subclassified high-grade B cell NHL		**121 (55.8)***
Diffuse large B cell	9680, 9684	106 (48.8)*
Burkitt	9687	13 (6.0)*
Precursor lymphoblastic B cell	9728	1 (0.5)*
Plasmablastic	9735	1 (0.5)*
Subclassified low-grade B cell NHL		**64 (29.5)***
CLL/SLL	9823, 9670	40 (18.4)
Follicular	9690, 9695, 9698	12 (5.5)*
Marginal zone	9710, 9689, 9699	7 (3.2)*
Mantle cell	9673	3 (1.4)*
Lymphoplasmacytic	9671	2 (0.9)*
Subclassified T cell NHL		**15 (6.9)***
Anaplastic large T/Null cell	9714	5 (2.3)*
Mature T cell, NOS	9702	3 (1.4)*
Mycosis fungoides	9700	3 (1.4)*
Angioimmunoblastic T cell	9705	1 (0.5)*
Precursor T cell lymphoblastic	9729	1 (0.5)*
Natural killer/T cell	9719	1 (0.5)*
Sézary syndrome	9701	1 (0.5)*
Otherwise subclassified NHL		**17 (7.8)***
Composite Hodgkin and non-Hodgkin lymphoma	9596	8 (3.7)*
Precursor cell lymphoblastic, unknown cellular lineage	9727	8 (3.7)*
Disseminated Langerhans cell histiocytosis	9754	1 (0.5)*
All unclassified lymphoma		**299 (57.9)**†
Unclassified, graded NHL		**42 (8.1)**†
High-grade B cell, NOS	9591	4 (0.8)†
Low-grade B cell, NOS	9591	2 (0.4)†
High-grade, unknown cellular lineage, NOS	9591	24 (4.7)†
Low-grade, unknown cellular lineage, NOS	9591	12 (2.3)†
Unclassified NHL or lymphoma, not graded		**257 (48.6)**†
Unclassified NHL, NOS	9591	165 (32.0)†
Unclassified NHL or HL, NOS	9590	92 (17.8)†
Total cohort		**516 (100)**†

CLL/SLL, chronic lymphocytic leukaemia/small lymphocytic lymphoma; HL, Hodgkin lymphoma; ICD-O, International Classification of Diseases for Oncology; NHL, non-Hodgkin lymphoma; NOS, not otherwise specified.

*Percentage of all subclassified NHL.

†Percentage of total cohort.

immunohistochemistry (IHC) diagnostics or cytogenetics due to lack of consistent data. Furthermore, we revised availability of Stage, B symptoms, ECOG PS, HIV status and any imaging. Biochemical evaluation such as lactate dehydrogenase, full blood count, comprehensive metabolic panel and International Prognostic Index were not consistently available either.

We adjusted the proportion of the age-groups within our younger cohort to that of the Surveillance, Epidemiology and End Results (SEER) cohort 1975–2016 (Howlader *et al.*, 2019) (age-standardisation) to compare the lymphoma subtype distribution irrespective of the age-effect with the SEER cohort. For statistical analysis, we used the Statistical Package for the Social Sciences (SPSS®), version 25 (SPSS Inc., IBM Corp., Armonk, NY, USA).

Use of secondary data and ethical approval was granted in accordance with each registry's regulations and by Martin-Luther-University Halle-Wittenberg. The study protocol is in line with the Declaration of Helsinki.

Results

A total of 516 patients from 11 registries ranging between one patient (Cotonou) and 70 patients (Addis Ababa) were included. Clinical and pathology records could be traced for 293 (56.8%). We were able to trace clinical records of 293 patients. Completeness of our data is shown in Fig S1. We amended the most valid base of diagnosis for 51 patients. For 36 patients with clinical or unknown base of diagnosis only registered, we found cytological diagnosis for seven, and histological diagnosis for 29. For 15 patients with cytological diagnosis registered, we found histological diagnosis and amended base of diagnosis accordingly. After reviewing clinical and pathological records, we amended pathological diagnosis for 59 patients, and identified Working Formulation diagnoses in 41 patients with unclassified NHL. Of these, 34 were assigned to either high- or low-grade NHL, the remaining seven patients to unclassified NHL, NOS.

For 299 patients of the total cohort (57.9%) no subclassification was identified. Among these, 207 (69.2%) were unclassified NHL (ICD-O code 9591). For the other 92 (30.8%), diagnosis did not include distinction between NHL and Hodgkin lymphoma [ICD-O code 9590 (Malignant lymphoma, NOS)]. For these, diagnosis of Hodgkin lymphoma can thus not be ruled out, although this is far less likely than NHL due to its relatively lower incidence in SSA (Bray *et al.*, 2018). Subclassification was identified for 217 patients of the total cohort (42.1%). The diagnoses in the 516 patients were confirmed histologically in 76.2%, with FNAC only in 17.3% and clinically without specimen analysis in 6.5%. Histologically diagnosed cases were subclassified in 186 of 366 (50.8%), cytologically diagnosed cases in 31 of 83 (37.3%). No clinically diagnosed cases were subclassified.

In Fig 3, quality of pathological diagnosis stratified by PBCRs is shown. According to NCCN guidelines harmonised for SSA, we defined diagnosis as most precise when NHL subclassification was available. Reliability of subclassification was considered better for histological confirmation than for FNAC confirmation only. In the absence of subclassification,

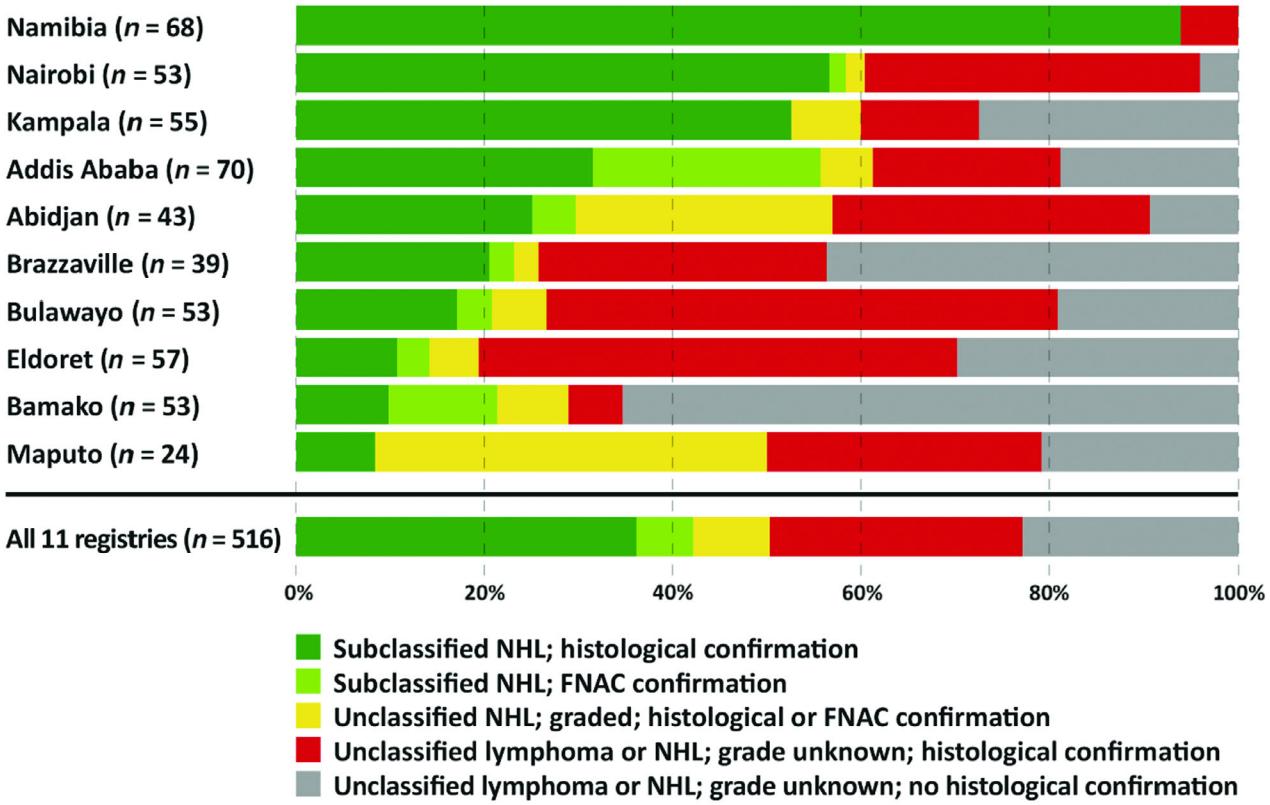


Fig. 3. Quality of pathological diagnosis. Stratified by population-based cancer registries, in order of quality of pathological diagnosis. With respect to non-Hodgkin lymphoma (NHL) subclassification, grade and diagnostic modality [according to National Comprehensive Cancer Network guidelines harmonised for Sub-Saharan Africa (Zelenetz *et al.*, 2019)]. Patients with morphologically ascertained diagnosis suitable for therapeutic decision-making (green and yellow): Patients with histopathological (dark green) or cytological (bright green) confirmation of subclassified NHL. Patients with unclassified but graded NHL (yellow). Patients with morphologically ascertained diagnosis not suitable for therapeutic decision-making (red): Patients with histological confirmation of lymphoma and neither subclassification nor grade. Patients with inconclusive diagnosis (white): Patients without histological confirmation of lymphoma and neither subclassification nor grade. (Cotonou was excluded from the figure due to small sample size, $n = 1$). FNAC, fine needle aspiration cytology. [Colour figure can be viewed at wileyonlinelibrary.com]

information on grade was deemed sufficient for basic therapy decision-making. For unclassified lymphoma with grade unavailable, histological confirmation of the disease was considered superior to other diagnostic modalities. In four registries, Namibia, Nairobi, Addis Ababa and Kampala, half or more NHLs were subclassified (94.1%, 58.5%, 55.7% and 52.7%, respectively). Bamako, Bulawayo, Eldoret and Maputo registries had the lowest proportion of NHLs subclassified (20.8%, 20.8%, 14.0% and 8.3%, respectively). Of the 299 unclassified cases, 123 (41.1%) were lacking histological confirmation.

Among the 217 subclassified NHLs, 20 subtypes were identified. We found a distribution of 55.8% high-grade B cell, 29.5% low-grade B cell, 6.9% T cell and 7.8% otherwise subclassified NHL. Diffuse large B cell lymphoma (DLBCL, ICD-O code 9680 and 9684) was the most common subtype (48.8%), followed by chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL, ICD-O code 9823 and 9670, 18.4%) and Burkitt lymphoma (BL, ICD-O code 9687, 6.0%). Rare entities such as various T cell NHL, primary central nervous system lymphoma (ICD-O code 9680), and extranodal unclassified lymphoma (ICD-O code 9590) suspicious of primary effusion lymphoma (ICD-O code 9678), were observed.

A moderate correlation between HIV prevalence in PBCRs and HIV-associated NHL was found (Table S2 and Fig S2). The proportion of HIV-associated NHL ranged between 38.5% and 89.1% in PBCRs with high HIV prevalence. For the remainder with lower prevalence, subtypes not associated with HIV were predominant.

Patients with high-grade B cell NHL had a median age of 43 years, patients with low-grade B cell NHL and T cell NHL were aged 52 and 56 years, respectively. When adjusting age-group proportions of our cohort to that of SEER, we found 41.4% DLBCL compared to SEER 27.8%, 25.4% for CLL/SLL compared to SEER 24.2% and 3.8% for BL compared to SEER 1.2% (Table S3).

Demographics, diagnostic modality and clinical presentation are shown in Table III. We found 88 of 473 NHLs to be primary extranodal lymphomas (18.6%) (Table S4).

Table III. Demographics, diagnostic modality and clinical presentation.

	High-grade B cell NHL	Low-grade B cell NHL	T cell NHL	All other lymphoma	Total cohort
Sex, *n* (%)					
Female	52 (41.6)	22 (33.3)	7 (46.7)	143 (46.1)	224 (43.4)
Male	73 (58.4)	44 (66.7)	8 (53.3)	167 (53.9)	292 (56.6)
Age, years					
Median (range) *n* (%)	43 (15–93)	52 (17–83)	56 (23–87)	42 (15–93)	45 (15–93)
15–39	50 (40.0)	15 (22.7)	4 (26.7)	133 (42.9)	202 (39.1)
40–59	56 (44.8)	24 (36.4)	5 (33.3)	119 (38.4)	204 (39.5)
≥60	19 (15.2)	27 (40.9)	6 (40.0)	58 (18.7)	110 (22.3)
Diagnostic modality, *n* (%)					
Histology	115 (92.7)	45 (73.8)	15 (100.0)	191 (68.2)	366 (76.2)
FNAC	9 (7.3)	16 (26.2)	0	58 (20.7)	83 (17.3)
Clinical	0	0	0	31 (11.1)	31 (6.5)
Unknown	1	5	0	30	36
Primary site involved, *n* (%)					
Nodal	97 (79.5)	36 (72.0)	8 (57.1)	244 (85.0)	385 (81.4)
Extranodal	25 (20.5)	14 (28.0)	6 (42.9)	43 (15.0)	88 (18.6)
Unknown	3	16	1	23	43
B symptoms*, *n* (%)					
No	9 (26.5)	2 (22.2)	2 (50.0)	6 (13.3)	19 (20.7)
Yes	25 (73.5)	7 (77.8)	2 (50.0)	39 (86.7)	73 (79.3)
Unknown	91	57	11	265	424
ECOG PS Score*, *n* (%)					
0 or 1	22 (40.7)	11 (64.7)	1 (33.3)	17 (29.3)	51 (38.6)
≥2	32 (59.3)	6 (35.3)	2 (66.7)	41 (70.7)	81 (61.4)
Unknown	59	49	12	252	384
Stage*, *n* (%)					
Early	22 (33.3)	4 (18.2)	3 (42.9)	19 (22.9)	48 (27.0)
Advanced	44 (66.7)	18 (81.8)	4 (57.1)	64 (77.1)	130 (73.0)
Unknown	59	44	8	227	338
HIV*, *n* (%)					
Negative	17 (29.8)	10 (76.9)	2 (66.7)	28 (34.6)	57 (37.0)
Positive	40 (70.2)	3 (23.1)	1 (33.3)	53 (65.4)	97 (63.0)
Unknown	68	53	12	229	362
Imaging*, *n* (%)					
CT/MRI/bone scan	17 (17.2)	4 (9.3)	2 (22.2)	13 (9.2)	36 (12.3)
X-ray and/or US	32 (32.3)	8 (18.6)	2 (22.2)	41 (28.9)	83 (28.3)
None	50 (50.5)	31 (72.1)	5 (55.6)	88 (62.0)	174 (59.4)
Unknown	26	23	6	168	223

CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FNAC, fine needle aspiration cytology; HIV, human immunodeficiency virus; MRI, magnetic resonance imaging; NHL, non-Hodgkin lymphoma; US, ultrasonography.

Stratified by high-grade B cell NHL [*n* = 125, including high-grade B cell NHL, not otherwise specified (*n* = 4)], low-grade B cell NHL [*n* = 66, including low-grade B cell NHL, not otherwise specified (*n* = 2)], T cell NHL (*n* = 15) and all other lymphoma (*n* = 310). Lugano Stage I, II, Binet Stage A and B were considered early disease, Lugano Stage III, IV and Binet Stage C advanced disease. We did not include patients with unknown clinical information in calculating percentage rates.

*Information for traced patients (*n* = 293) available only.

For 293 patients with clinical records traced, information on ECOG PS, B symptoms, Stage and HIV testing were available for 45.1%, 31.4%, 60.8%, and 52.6%, respectively. ECOG PS of ≥2 was documented in 61.4%, and 79.3% presented with B symptoms. In all, 73.0% were diagnosed with advanced Stage III or IV. HIV infection was documented for 63.0%. Imaging was done for 40.6%.

In Fig 4, quality of clinical diagnosis stratified by PBCRs is shown. According to NCCN guidelines harmonised for SSA, five clinical criteria are, among others, necessary for NHL diagnosis: ECOG PS, information on B symptoms, Stage, HIV status and any imaging done (Zelenetz *et al.*, 2019). Only 6.1% fulfilled all five criteria. On average 2.3 clinical criteria were available. Clinical diagnostics were most comprehensive in Kampala, with 9.1% meeting all five clinical criteria and on average 3.5 clinical criteria available. In Eldoret, Addis Ababa and Nairobi registries, clinical criteria were particularly lacking, with 1.7, 1.6 and 0.8 available on

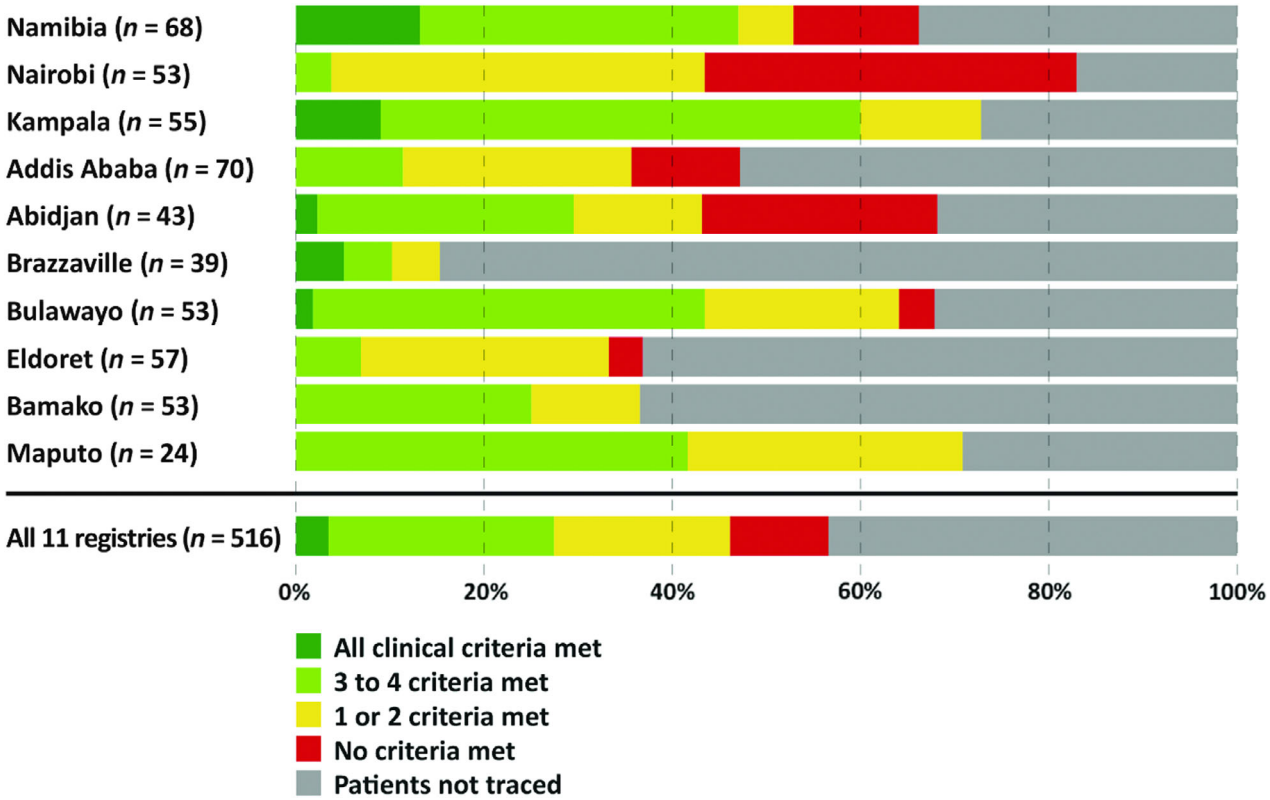


Fig. 4. Completeness of clinical diagnostic criteria. Stratified by population-based cancer registries, in order of Figure 3. With respect to information on Eastern Cooperative Oncology Group Performance Status, B symptoms, human immunodeficiency virus status, stage and any imaging [according to National Comprehensive Cancer Network guidelines harmonised for Sub-Saharan Africa (Zelenetz *et al.*, 2019)]. This information was only available for patients traced. (Cotonou was excluded from the figure due to small sample size, $n = 1$). [Colour figure can be viewed at wileyonlinelibrary.com]

average, respectively. Of the total cohort, 51.2% met two or fewer criteria only.

Discussion

Unclassified lymphoma cases and diagnostic modality

The NCCN has recognised the need to guide SSA physicians in resource-constrained settings and has published harmonised guidelines on a variety of B cell lymphomas (Zelenetz *et al.*, 2019). For the wide range of NHL entities, a broad spectrum of subtype-specific therapeutic algorithms has been designed. This requires NHL subclassification, as there are no recommendations on treatment of unclassified lymphoma. In this regard, the high proportion of 57.9% of unclassified lymphoma is striking. Distribution of unclassified lymphoma differed strongly among registries, ranging between Maputo (91.7%) and Namibia (5.9%). The varying quality of pathological diagnosis indicates that NHL diagnostic routine does not yet reach minimum standards for many patients. It is notable that for one in six patients, FNAC, and for one in 15 patients, clinical information only was the basis of the NHL diagnosis. Half of patients with NHL with histological confirmation had no subtype available, for patients with FNAC confirmation, the proportion was even higher (64.7%). The wide-spread use of FNAC in SSA has also been reported by others (Naresh *et al.*, 2011; Lemos *et al.*, 2018). FNAC is cheaper than core needle biopsy and much easier than surgical resection. However, as many investigators state, including the NCCN SSA guidelines, cytological diagnosis, let alone clinical presentation only, is deemed insufficient for NHL diagnosis except for CLL (Naresh *et al.*, 2011; Wilkins, 2011; Lemos *et al.*, 2018; Zelenetz *et al.*, 2019).

Biopsy material is mandatory for almost all kinds of pathological evaluation. Due to high cost and demanding infrastructure, IHC has yet to be facilitated in most SSA countries. Molecular genetics are practically unavailable. Consequentially, pathologists mostly rely on haematoxylin and eosin stains (Lemos *et al.*, 2018).

Hospital-based studies have reported much lower rates of unclassified lymphoma (13–14%) (Bateganya *et al.*, 2011; Milligan *et al.*, 2018). The severe lack of proper characterisation of lymphoma in our present cohort may be explained by lack of pathological infrastructure (Cainelli *et al.*, 2010; Wiggill *et al.*, 2013). Scarcity of trained personnel, especially

pathologists, is another major issue in SSA (Benediktsson *et al.*, 2007; Adesina *et al.*, 2013). In the Republic of Congo, for example, there is one pathologist available for the entire country with >4 million inhabitants (Jean-Félix Péko, 2019). The importance of correct classification of NHL remains an unmet need in SSA (Naresh *et al.*, 2011). Development and consistent implementation of resource-conserving guidelines on basic diagnostic procedures should be considered. The recent updates of the harmonised NCCN guidelines may lead to diligent and feasible subclassification algorithms for NHL in resource-constrained health systems. Hence, subtype-directed treatment could be enabled for a higher proportion of NHL. With limited resources, Malawian pathologists, for example, have reached concordance rates with American diagnoses of >90%, relying on basic cytology and histology services, a small IHC panel of nine antibodies and a telepathology conference (Montgomery *et al.*, 2016).

Subtypes of non-Hodgkin lymphoma

The relatively high percentage of high-grade B cell NHL (55.8%) observed in our present study confirms other studies from SSA (Naresh *et al.*, 2011; Wiggill *et al.*, 2011; Wiggill *et al.*, 2013; Patel *et al.*, 2015; Montgomery *et al.*, 2016; Perry *et al.*, 2016a; Milligan *et al.*, 2018). DLBCL (ICD-O code 9680 and 9684), BL (ICD-O code 9687), plasmablastic lymphoma (ICD-O code 9735), primary central nervous system lymphoma (ICD-O code 9680), and unclassified extranodal lymphoma suspicious of primary effusion lymphoma (ICD-O code 9678) were observed. All of these aggressive subtypes mentioned are associated with HIV (Re *et al.*, 2019), partly explaining their high proportion in our present study. However, in other parts of the resource-constrained world with much lower HIV prevalence than SSA, high-grade B cell NHLs are also known to be frequent. High-grade B cell NHL incidence is lower in the multicentric, population-based SEER study (31.3%) (Howlader *et al.*, 2019). This indicates that besides higher burden of further infectious diseases such as EBV (Crawford *et al.*, 2014), environmental and other factors such as demographics may play a role as well (Perry *et al.*, 2016a).

However, we could show that when age-adjusting our present cohort to the SEER cohort (Howlader *et al.*, 2019), proportions of DLBCL and BL remained lower in the SEER cohort (DLBCL adjusted: 41.4%, SEER: 27.8%; BL adjusted: 3.8%, SEER: 1.2%, respectively). HIV prevalence varied across the 11 participating PBCRs. Nairobi, Abidjan, Kampala, Namibia, Bulawayo and Maputo had high HIV prevalence (4.9–16.9%); whereas prevalence for the remaining PBCRs was much lower (1.7–4.1%) (National AIDS and STI Control Programme (NASCOP), 2012; United Nations Joint Programme on HIV/AIDS (UNAIDS), 2018; The Demographic and Health Surveys (DHS) Program, 2019). This affects proportions of HIV-associated lymphoma (89.1% in Namibia, 64.5% in Nairobi, 51.7% in Kampala *versus* 25.6% in Addis Ababa and 27.3% in Bamako). When testing for heterogeneity, Fig S2 shows that HIV prevalence in registries did moderately correlate with the respective proportion of HIV-associated NHL. There are numerous reasons that may increase or decrease the ratio of HIV-associated NHL in respective registries with varying HIV prevalence, including availability and reliability of detailed diagnosis, stigma of HIV-infected patients and quality of service for HIV patients.

The low frequency for CLL/SLL is consistent with other studies on NHL subtype distribution in SSA (Wiggill *et al.*, 2011; Perry *et al.*, 2016a) When age-adjusting to the SEER cohort, however, the proportion of CLL/SLL approximated the SEER proportion (CLL/SLL adjusted: 25.4%, SEER: 24.2%). Patients diagnosed with high-grade B cell NHL were diagnosed at a young age (median 43 years) compared to low-grade B cell NHL and T cell NHL patients (median age 52 and 56 years, respectively). The high burden of young patients diagnosed with aggressive NHL represents a socioeconomic threat and efficient treatment could reduce impact on SSA economies. Prospective, hospital-based studies in HIV-prevalent settings have shown that treatment for NHL can be safe, effective and feasible. The 1-year overall survival, regardless of NHL subtype, in Botswana was 53.7%. For DLBCL in Malawi, the 2-year progression-free survival was 34% (Milligan *et al.*, 2018; Painschab *et al.*, 2019)."

Clinical presentation

Patients with NHL in SSA present late, with nearly three-quarters diagnosed at advanced stage, almost two-thirds scoring an ECOG PS of ≥2, and four out of five suffering from B symptoms in our present cohort. Results are comparable to another retrospective, hospital-based study from the Uganda Cancer Institute (Bateganya *et al.*, 2011). The issue of late disease recognition due to lack of diagnostic resources, misdiagnosis (Buyego *et al.*, 2017), poor referral mechanisms, financial woes, low awareness and poverty may add to late presentation in the SSA tertiary hospital setting (Mwamba *et al.*, 2012). Even in Botswana, a middle-income country, duration between initial NHL symptoms and eventual diagnosis of NHL was 280 days on average (Milligan *et al.*, 2018). The proportion of primary extranodal disease was 18.6% in our present cohort. Even after carefully reviewing clinical records, our present data on extranodal organ manifestation of NHL may be confounded by primary nodal NHL infiltrating extranodal organs. Patients with extranodal lymphoma were possibly not diagnosed due to lack of comprehensive imaging such as computed tomography, let alone positron emission tomography, and absence of imaging in 59.4% of traced patients. However, in case of doubt, we assigned NHL as primary nodal rather than extranodal disease. Moreover, lack of imaging may also lead to understaged NHL within our present cohort, for which more sophisticated staging would have revealed even more advanced disease stages. A review has reported classification

of primary extranodal lymphoma to be inconsistent on a global scale (Vannata & Zucca, 2015), which may impede comparability with other studies in SSA. Mostly, these studies have reported higher proportions of extranodal disease; however, they did not specify whether extranodal disease was primary or secondary (Mwamba *et al.*, 2012).

In the absence of imaging procedures like ultrasonography, X-ray, and even less available higher-cost imaging procedures, thorough physical examination is essential. We found a high proportion of traced patients that lacked imaging and staging (59.4%, and 39.2%). Furthermore, lack of HIV testing in 139 patients (47.4% of 293) has to be noted. Due to these shortfalls, a median of only 2.3 of the five baseline non-pathological diagnostic criteria recommended by the harmonised NCCN guidelines were available. Stage, HIV status, and ECOG PS are key determinants for treatment. Improving completeness of patient examination could enhance personalised therapy decision-making and outcome.

Strengths and limitations of our study

The present study has several strengths. First, our initial total population-based cohort ($n = 599$) comprised 56.1% of all 1068 patients with NHL registered in the 11 PBCRs during the period of randomisation, of which we traced the clinical records of 293 patients. Second, the geographical variety of countries allows for an overview of patients with NHL with different ethnicities living in different socioeconomic settings, with both high and low HIV and malaria prevalence. Third, the patients were a random sample of all adult NHL cases, from both public and private institutions, treated or untreated, and we considered all bases of diagnosis, whether made histologically or solely clinically. The present study is, in fact, the first population-based overview of clinical presentation and diagnostics of patients with NHL in real-world SSA.

The present study also has several limitations. First, population-based cancer registries are limited by data quality (Parkin *et al.*, 2018). For example, 52 patients (8.7%) that were registered as NHL in the PBCR databases did not actually have a NHL diagnosis in their clinical records. For patients with traced clinical records (56.8%), we could amend these shortfalls and exclude such patients. Second, all of the PBCRs with the exception of Namibia cover urban populations and do not reflect experience in rural areas (Crocker-Buque & Pollock, 2015), but they provide the broadest image available of NHL patients' reality across the 10 countries participating. Third, we expect misclassified lymphoma in our present cohort. Deviations between diagnosis of general pathologists and expert haemato-pathologists are common in SSA, but occur also in high-income settings (Clarke *et al.*, 2004; LaCasce *et al.*, 2008; Chang *et al.*, 2014; Herrera *et al.*, 2014), including assignment to wrong cellular lineage (Armitage, 2013; Herrera *et al.*, 2014; Lage *et al.*, 2015) or even confounding benign and malignant disease (Wilkins, 2011; Ayers *et al.*, 2012; Masamba *et al.*, 2016; Buyego *et al.*, 2017). Two expert re-evaluations of lymphoma tissue in SSA have described diagnostic accuracy of 75% and 78%, respectively, reporting on poor tissue quality and frequent misdiagnoses (Naresh *et al.*, 2011; Ogwang *et al.*, 2011). Fourth, results on subtypes reported in our present study are hampered by different classification systems as outdated as the Working Formulation. We consider subtype distribution within our present cohort reliable nonetheless because we only considered outdated lymphoma subclassifications that allowed for obvious conversion to the current classification system. Fifth, a major issue to data analysis represented the rate of clinical records traced, 56.8%. We believe that clinical records were either, missing at random because of handwritten records, misspelling of names and inconsistent archive quality, or missing when records were not initiated in patients without clinical therapy. Even when clinical records could be assessed, we found a high proportion of missing data. However, this seems to be a general problem in the SSA setting as in a single-centred retrospective study and even in another multicentre prospective study, Stage was missing for 40% and 28% of patients, respectively (Bateganya *et al.*, 2011; Milligan *et al.*, 2018).

Conclusion

Our present pilot study describes NHL subtype distribution and diagnostic service received for patients on a population-level. As both pathological, as well as clinical diagnostics, are incomplete in most patients, thorough implementation of the NCCN guidelines harmonised for SSA remains challenging in many countries. Development of diagnostic algorithms emphasising feasibility in resource-constrained settings, improvement of laboratory infrastructure (especially IHC), and training of pathology and oncology workforce is required for more accurate diagnosis. Only then can sensible decision-making on guideline-adherent treatment be implemented for patients with NHL in SSA. The effect of such measures in real-world SSA should be monitored applying population-based research.

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Author contributions

All authors contributed to the contents and revised the article. Annelle Zietsman, Jean-Félix Péko, Fisihatsion Tadesse, Nathan G. Buziba, Henry Wabinga, Mary Nyanchama, Margaret Z. Borok, Mamadou Kéita, Guy N'da, Cesaltina F. Lorenzoni and Marie-Thérèse Akele-Akpo were responsible for the provision of data. Nikolaus C.S. Mezger and Eva J. Kantelhardt designed the study, did the data analysis, interpreted the data, and wrote the article. Cornelia Gottschick, Mascha Binder, Jörg Mezger, Ahmedin Jemal, Donald Maxwell Parkin and Claudia Wickenhauser did the data analysis, interpreted the data and wrote the article. Mirko Griesel, Lucia Hämmerl, Tobias P. Seraphin, Jana Feuchtner, interpreted the data.

Conflicts of interest

The authors declare no competing financial interests. Eva J. Kantelhardt has received travel support from Daiichy Sankyo.

Supporting Information

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

Fig S1. Completeness of data. All areas relative to black rectangle (NHL patients registered, n = 1068). Red: pathological (cytological or histological) confirmation of NHL *only*; yellow: any clinical data on HIV, stage, ECOG PS B symptoms or imaging *only*; orange: *both* pathological confirmation of NHL *and* any clinical data present. For patients not traced (n = 223), only registry data on demographics and pathological diagnosis were available. For these, no data on clinical information on stage, HIV status etc. were available. ECOG PS, Eastern Cooperative Oncology Group Performance Status; NHL, non-Hodgkin lymphoma.

Fig S2. Correlation between HIV prevalence for PBCR and HIV-associated NHL among subclassified NHL. Correlation coefficient was r = 0,605 (p value = 0.064). HIV prevalence for 15-49 year old populations was extracted from online data bases (National AIDS and STI Control Programme (NASCOP), 2012; United Nations Joint Programme on HIV/AIDS (UNAIDS), 2018; The Demographic and Health Surveys (DHS) Program, 2019). PBCR, population-based cancer registry; NHL, non-Hodgkin lymphoma.

Table S1. ICD-10 codes included in study for patient selection (April *et al,* 2013).

Table S2. Proportion of HIV-associated non-Hodgkin lymphoma among subclassified non-Hodgkin lymphoma. Stratified by registry and HIV prevalence. HIV prevalence for 15-49 year old populations was extracted from online data bases (National AIDS and STI Control Programme (NASCOP), 2012; United Nations Joint Programme on HIV/AIDS (UNAIDS), 2018; The Demographic and Health Surveys (DHS) Program, 2019).

Table S3. Age-adjustment of non-Hodgkin lymphoma (NHL) subtypes found in our cohort to Surveillance, Epidemiology and End Results (SEER) cohort 1975-2016 (Howlader *et al,* 2019). Age 15-19 in our cohort (n=27) and 0-19 in SEER cohort (n=14.312) were excluded for analysis. Subsequently, unclassified NHL (International Classification of Diseases for Oncology (ICD-O) morphology code 9591 (April *et al,* 2013)) and unclassified lymphoma or NHL (9590) were excluded for our cohort (n=272) and for SEER (n=11.752) when calculating proportions.

Table S4. Primary extranodal lymphoma. Stratified by topographic categories (April *et al,* 2013) and lymphoma types.

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