The pathway to diagnosis of Hodgkin Lymphoma in a HIV and TB-endemic setting

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BACKGROUND

- Accurate data on the incidence, clinical presentation and outcomes of lymphoma in sub-Saharan Africa are scarce, likely due to under-diagnosis and under-reporting of cases.
- The incidence of Hodgkin lymphoma (HL) is increased in HIV infection by 5-7 fold, despite ART[1].
- Lymphoma in the first-world setting is associated with a long delay in diagnosis due to vague symptomatology and insidious onset of symptoms, the poor sensitivity of the fine-needle aspirate (FNA) to diagnose lymphoma and lack of a distinct referral pathway for lymphadenopathy that will lead to a tissue diagnosis[2].
- The difficulty in diagnosis of HL is further complicated by overlapping symptomatology and diagnostic difficulty with extrapulmonary TB (EPTB). Both TB and HL may present with lymphadenopathy, B symptoms, cytopenias and have overlapping features on histology (such as poorly formed granulomas).
- An alarmingly high number of lymphoma patients are on TB therapy at lymphoma diagnosis in South Africa, in the majority of cases, this is a **presumptive therapy,** and in a lower proportion patients have a proven TB diagnosis. Cohort studies in South Africa report that 25-88% of patients with newly diagnosed lymphoma, and 72% of patient with HIV infection and HL are on TB therapy at the time of diagnosis of lymphoma.

OBJECTIVES

- To describe the pathway to diagnosis in patients with HL referred to Groote Schuur Hospital, Cape Town by critical time intervals identified as:
  - Patient interval (symptom onset to seeing first doctor)
  - Healthcare Practitioner Interval (doctor to diagnostic biopsy)
  - Referral interval (diagnostic biopsy to specialist clinic)
  - Treatment interval (specialist clinic to chemotherapy)
- To compare the time to diagnosis of HL to aggressive NHL
- To assess the impact of TB therapy and the fine-needle aspirate in contributing to diagnostic delay
- To assess the impact of diagnostic delay on mortality

METHODS

- Patient population: adult patients diagnosed with HL and NHL between Jan 2012- April 2014 and referred to GSH. Burkitt lymphoma and lymphoblastic lymphoma were excluded.
- Information regarding diagnosis, demographic details and biopsy dates were taken from patient clinic folder records.
- Information regarding symptomatology was obtained via semi-structured interviews in 80 patients (telephonically or in person), and in a further 53 patients from clinical records (these patients were either not contactable or deceased.
- Pathway to diagnosis was divided into time intervals as described above.
- Survival was assessed at 1st November 2017, overall survival curves were constructed using the Kaplan-Meier method.
- Categorical and continuous variables were summarised with frequencies and means or medians and inter-quartile ranges respectively. Univariate comparisons between categorical variables were performed with the chi-squared test. Multivariate logistical regression analysis was performed to calculate OR to assess the association between clinically relevant covariates and delays in diagnosis and treatment.

RESULTS

Sample Characteristics and Clinical Presentation

Table I. Sample characteristics and disease presenting features

	All (n=163)		HIV - (n=116)		HIV + (n=47)		P-value	NHL (n=122)		HL (n=41)		P-value
Sex												
Male	94	58%	72	62%	22	47%	0.07	70	57%	24	59%	
Female	69	42%	44	38%	25	53%		52	43%	17	41%	0.90
Age												
Median (IQR)	48 (33-59)		54 (37-62)		38 (30-47)		<0.01	51 (38-61)		35 (28-45)		<0.01
<18	3	2%	3	3%	0	0%		2	2%	1	2%	
18-39	57	35%	30	26%	27	57%		34	28%	23	56%	
40-59	66	40%	46	40%	20	43%		52	43%	14	34%	
60-79	35	21%	35	30%	0	0%		32	26%	3	7%	
80 or older	2	1%	2	2%	0	0%		2	2%	0	0%	
Race												
Mixed ancestry	81	50%	77	66%	4	9%	<0.01	62	51%	19	46%	
Black	59	36%	18	16%	41	87%		40	33%	19	46%	
White	23	14%	21	18%	2	4%		20	16%	3	7%	0.18
Performance score												
ECOG 0	19	12%	14	12%	5	11%	0.97	11	9%	8	20%	
ECOG 1	74	45%	54	47%	20	43%		53	43%	21	51%	
ECOG 2	27	17%	19	16%	8	17%		21	17%	6	15%	
ECOG 3	32	20%	22	19%	10	21%		27	22%	5	12%	
ECOG 4	11	7%	7	6%	4	9%		10	8%	1	2%	0.17
Stage of disease at presentation												
Stage 1	23	14%	18	16%	5	11%	0.23	22	18%	1	2%	0.04
Stage 2	35	21%	27	23%	8	17%		28	23%	7	17%	
Stage 3	19	12%	10	9%	9	19%		13	11%	6	15%	
Stage 4	86	53%	61	53%	25	53%		59	48%	27	66%	
Bone marrow involved at diagnosis	41	25%	23	20%	18	38%	0.03	23	19%	18	44%	<0.01
Clinical presentation and investigations												
Peripheral lymphadenopathy	104	64%	73	63%	31	66%	0.72	69	57%	35	85%	<0.01
B Symptoms	96	59%	66	57%	30	64%	0.42	66	54%	30	73%	0.03
Diagnosis made on bone marrow	10	6%	5	4%	5	11%	0.66	4	3%	6	15%	0.23
On TB therapy at diagnosis	16	10%	4	3%	12	26%	<0.01	5	4%	11	27%	<0.01
FNAC												
Performed	63	39%	44	38%	19	40%	0.77	39	32%	24	59%	<0.01
Not performed	100	61%	72	62%	28	60%		83	68%	17	41%	

RESULTS

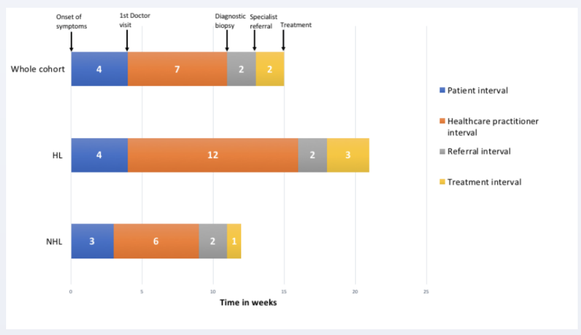

Table III. Factors associated with diagnostic delay in multivariable logistic regression

	OR (95% CI)	P-value
FNAC performed (vs not performed)	1.4 (0.7-3.1)	0.38
Late-stage (vs early-stage)	2.3 (1.1-5.2)	0.04
HL (vs NHL)	3.0 (1.1-8.0)	0.03
Emergency chemotherapy (vs non-emergency)	0.6 (0.2-1.5)	0.24
HIV positive (vs negative)	0.9 (0.3-2.2)	0.76
Age ≥50yr (vs <50yr)	1.6 (0.7-4.0)	0.30

- HL showed statistically significant longer time to diagnosis than NHL, and patients with HL were more likely to be on TB therapy at the time of diagnosis (p<0.01)
- 53% of patients experienced diagnostic delay > 6weeks and the longest period of delay was within the 'health care practitioner' interval.
- TB therapy lengthened the time of diagnosis by 4 weeks (10wk vs 6 wks), p=0.28
- FNA lengthened the time to diagnosis by 4 weeks (9wk vs 5 wks), p= 0.04
- OS was 46% (median survival 27 months), total follow up time of 3863months
- A longer time-to-diagnosis was not associated with poorer survival (sub-analysis of HL alone also did not show an association), but late-stage disease was associated both with diagnostic delay and a poorer OS.

Fig. 3. OS by type of lymphoma and HIV status

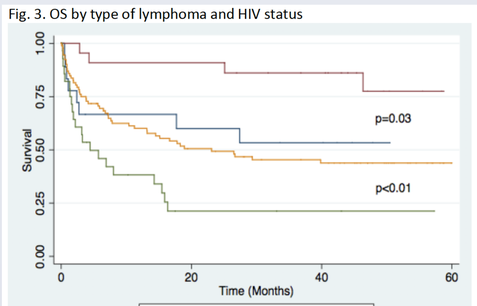

Table IV. Predictors (with hazard ratios) of OS by multivariable Cox regression analysis

	HR (95% CI)	P-value
Late-stage (vs early-stage)	2.0 (1.1-3.8)	0.03
NHL (vs HL)	2.5 (1.1-5.0)	0.05
Emergency chemotherapy (vs non-emergency)	1.2 (0.6-2.3)	0.70
HIV positive (vs negative)	4.2 (1.9-9.4)	<0.01
Performance status (vs ECOG = 0)		
ECOG 1	1.8 (0.5-6.3)	0.35
ECOG 2	3.7 (1.0-14.6)	0.06
ECOG 3	7.6 (2.1-27.4)	<0.01
ECOG 4	4.5 (1.1-17.6)	0.03
Diagnostic delay	0.6 (0.3-1.0)	0.06
Age ≥ 50 (vs <50)	4.1 (1.9-8.9)	<0.01

CONCLUSIONS AND DISCUSSION

- A high proportion of our patients are diagnosed with late-stage disease
- In HL the diagnosis is most likely to be delayed and patients are most likely to be on presumptive TB therapy
- Diagnostic delay likely did not show an association with survival, possibly due to
  - Recall bias (methodology)
  - Heterogeneity in lymphoma type and subtype
  - More aggressive disease present acutely, have a shorter time to diagnosis and have poor outcomes
- Healthcare Practitioner Interval is the longest time interval, lengthened by
  - High suspicion for TB, and presumptive TB therapy
  - Use of FNA (often repeated)
  - Barriers in accessing lymph node biopsies
- In Sub-Saharan Africa and other TB-endemic areas, targeted interventions are needed to improve the diagnosis of lymphoma (both in improving detection rates as well as decreasing the time-to-diagnosis). These may include implementation of **rapid access LN biopsy clinics**, **patient and physician education** regarding the significance of lymphadenopathy and **investigative algorithms** specific to a TB-endemic area (including the role of new TB molecular diagnostic tests on lymph node tissue)

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