

TO THE EDITOR:

Treatment delays in children and young adults with lymphoma: a report from an East Africa lymphoma cohort study

William Frank Mawalla,¹ Liz Morrell,² Lulu Chirande,¹ Caroline Achola,³ Hadija Mwatemi,⁴ Godlove Sandi,⁴ Salama Mahawi,⁴ Atukuzwe Kahakwa,⁵ Paul Ntemi,⁶ Nabalende Hadija,³ Elifuraha Mkwizu,⁵ Clara Chamba,¹ Dimitris Vavoulis,⁷ and Anna Schuh^{1,7}

¹AI-REAL Study, Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania; ²Health Economics Research Centre, Nuffield Department of Population Health, University of Oxford, Oxford, United Kingdom; ³AI-REAL Study, St Mary's Hospital Lacor, Gulu & African Field Epidemiology, Gulu-Uganda, Northern Region, Uganda; ⁴AI-REAL Study, Muhimbili National Hospital, Dar es Salaam, Tanzania; ⁵AI-REAL Study, Kilimanjaro Christian Medical Centre, Moshi, Tanzania; ⁶AI-REAL Study, Bugando Medical Centre, Mwanza, Tanzania; and ⁷AI-REAL Study, Department of Oncology, University of Oxford, Oxford, United Kingdom

Lymphomas are a diverse group of hematopoietic neoplasms resulting from the malignant transformation of lymphoid cells and their precursors.¹ If diagnosed early and precisely, most lymphomas in children and young adults have excellent cure rates of up to 90% using affordable treatments from the essential medicine list by the World Health Organization.²⁻⁶ In contrast, prolonged time-to-diagnosis and treatment usually results in poor treatment outcomes, especially in aggressive lymphoma types.⁷ In sub-Saharan Africa (SSA), cited causes of delay in diagnosis and treatment are low socioeconomic status, poor health-seeking behavior and access to health care, an inefficient health care referral system, a shortage of trained experts, and limited diagnostic capability.^{8,9} Studies analyzing delays in the diagnosis and treatment of lymphoma in SSA are limited. An objective assessment of the time to definitive care and associated factors is crucial in identifying intervention points along the pathway to care for patients with lymphoma in resource-restricted regions.

Here, we present the results of a prospective multicenter study involving 2 East African countries that evaluates both patient and health care-related delays among children and young adults diagnosed with lymphoma. The study was conducted at 3 tertiary cancer hospitals in Tanzania and 1 cancer center, St Mary's Hospital-Lacor Hospital, in Northern Uganda. The centers in Tanzania included Muhimbili National Hospital in Dar es Salaam, Kilimanjaro Christian Medical Centre in Kilimanjaro, and Bugando Medical Centre in the Mwanza region, north of Tanzania. Ethical approval was granted by the Oxford Tropical Research Ethics Committee, the National Institute of Medical Research in Tanzania, the Uganda National Council of Science and Technology, and the Lacor Hospital Institutional Research Ethics Committee in Uganda. The AI-REAL study enrolled children and young adults (aged 3-30 years) presenting with suspected lymphoma. Here, we focus on the subset of patients with a biopsy-confirmed lymphoma diagnosis. For all enrolled patients, demographic and baseline clinical data, including the date they first experienced symptoms, the date they first visited a local health care center, and the date the local health care center referred them to the tertiary cancer center, were recorded. Upon arrival at the tertiary cancer treatment centers, the dates and times of tissue sampling, arrival of tissue in the pathology laboratory for processing and pathology reports (with and without immunohistochemistry), and start of definitive cancer treatment were recorded. The primary outcome was the median total treatment delay and its individual components. Total treatment delay was defined as the time from the onset of symptoms to the start of definitive cancer treatment. The total treatment delay included the time-to-first health care contact (from the onset of symptoms) to contact with the first health care facility, excluding the visit to traditional healers, time-to-referral (from the first health care facility contact to arrival at a cancer treatment center), and time-to-treatment after arrival at a cancer center (time from arriving at a cancer treatment center to receiving definitive cancer treatment). Time-to-diagnosis was defined as the time from arrival at a cancer center to receiving a tissue diagnosis report, either a morphology report alone or a morphology with immunohistochemistry (IHC) report.

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Data are available on request from the corresponding author, William Frank Mawalla (mawallawf@gmail.com).

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Table 1. Baseline characteristics of study participants

| Characteristic | Overall, N = 148 | BL, N = 65 | DLBCL, N = 37 | HL, N = 46 | P value* |
|--|---------------------|-----------------|------------------|----------------|------------------|
| Treatment center, no. (%) | | | | | < .001 |
| Rural Uganda | 39 (26) | 30 (46) | 4 (11) | 5 (11) | |
| Tanzania | 109 (74) | 35 (54) | 33 (89) | 41 (89) | |
| Age in y, median (IQR) | 12 (9-18) | 11 (7-14) | 15 (10-19) | 16 (9-20) | .003 |
| Sex, no. (%) | | | | | .10 |
| Female | 48 (32) | 15 (23) | 15 (41) | 18 (39) | |
| Male | 100 (68) | 50 (77) | 22 (59) | 28 (61) | |
| Distance (region) from the cancer center, no. (%) | | | | | .11 |
| Far | 68 of 144 (47) | 36/63 (57) | 15/37 (41) | 17/44 (39) | |
| Near | 76 of 144 (53) | 27/63 (43) | 22/37 (59) | 27/44 (61) | |
| A prior visit to the local healer, no. (%) | 85 (57) | 37 (57) | 21 (57) | 27 (59) | > .9 |
| HIV-positive, no. (%) | 7 of 111 (6.3) | 3/51 (5.9) | 4/27 (15) | 0/33 (0) | .053 |
| B-symptoms, no. (%) | 128 of 145 (88) | 56/64 (88) | 32/36 (89) | 40/45 (89) | > .9 |
| LDH levels (IU/L), median (IQR) | 700 (396-1156) | 960 (678-1587) | 613 (387-1436) | 549 (336-700) | < .001 |
| Cytopenias, no. (%) | 110 of 129 (85) | 50 of 60 (83) | 25 of 32 (78) | 35 of 37 (95) | .11 |
| Peripheral LAD, no. (%) | 101 of 143 (71) | 36 of 60 (60) | 23 of 37 (62) | 42 of 46 (91) | < .001 |
| Jaw mass, no. (%) | 48 of 147 (33) | 32 of 64 (50) | 10 of 37 (27) | 6 of 46 (13) | < .001 |
| Mediastinal mass, no. (%) | 24 of 105 (23) | 3 of 43 (7.0) | 6 of 24 (25) | 15 of 38 (39) | .002 |
| Abdominal mass, no. (%) | 65 of 123 (53) | 31 of 53 (58) | 10 of 29 (34) | 24 of 41 (59) | .077 |
| Site of biopsy, no. (%) | | | | | < .001 |
| Abdomen | 40 of 138 (29) | 26 of 62 (42) | 14 of 34 (41) | 0 of 42 (0) | |
| Peripheral node | 90 of 138 (65) | 32 of 62 (52) | 17 of 34 (50) | 41 of 42 (98) | |
| Other deeper tissue regions | 8 of 138 (5.8) | 4 of 62 (6.5) | 3 of 34 (8.8) | 1 of 42 (2.4) | |
| Clinical stage, no. (%) | | | | | .4 |
| Stage I/II | 44 of 145 (30) | 23 of 63 (37) | 11 of 36 (31) | 10 of 46 (22) | |
| Stage III | 65 of 145 (45) | 24 of 63 (38) | 15 of 36 (42) | 26 of 46 (57) | |
| Stage IV | 36 of 145 (25) | 16 of 63 (25) | 10 of 36 (28) | 10 of 46 (22) | |
| Change in initial morphology-only diagnosis after IHC, no. (%) | 24 of 116 (20.7) | 12 of 53 (22.6) | 8 of 28 (28.6) | 4 of 35 (11.4) | .222 |

P value < 0.05 was considered statistically significant and is indicated in bold.

*Pearson χ^2 test; Kruskal-Wallis rank sum test; Fisher exact test; LDH, lactate dehydrogenase; peripheral LAD, peripheral lymphadenopathy.

Between 1 May 2019 and 25 September 2022, 291 patients with suspected lymphoma were enrolled. Of these, 148 had a confirmed lymphoma diagnosis, completed follow-ups, and were included in the final analysis. The baseline characteristics of 148 patients with lymphoma who received cancer treatment are shown in Table 1. Most patients (74%) came from Tanzania cancer centers. The median age of patients was 12 years (interquartile range [IQR], 9-18), and 100 (68%) were males. Only 85 of 148 patients (57%) had visited a traditional healer. Seven of 111 patients (6.3%) were tested as HIV-positive, and 101 of 145 patients (70%) presented with advanced disease (stage III or IV disease).

The median total treatment delay for the entire cohort was 124 days (95% confidence interval [95% CI], 107-136; Figure 1A). The probability of treatment not started for the entire cohort was 64% (95% CI, 56-72) at 90 days and 30% (95% CI, 24-39) at 180 days. The median total treatment delay for those with Burkitt lymphoma (BL) was 91 days (95% CI, 80-115), whereas for diffuse large B-cell lymphoma (DLBCL) and Hodgkin's lymphoma (HL), it

was 114 days (95% CI, 84-148) and 232 days (95% CI, 179-305), respectively (P value < .0001; Figure 1B). The probability of treatment not started for BL was 51% (95% CI, 40-65) at 90 days and 12% (95% CI, 6.4-24) at 180 days. For DLBCL, the probability of treatment not started was 59% (95% CI, 46-78) at 90 days and 24% (95% CI, 14-43) at 180 days; whereas for HL, it was 85% (95% CI, 75-95) at 90 days and 61% (95% CI, 48-77) at 180 days.

Analysis of the different components of total treatment delay (Figure 1C) showed a median time-to-first health care facility contact of 32 days (IQR, 12-65), a median time-to-referral of 37 days (IQR, 14-83), and a median time-to-treatment after arrival to the cancer center of 17 days (IQR, 9-28). With respect to delay in secondary and tertiary care, the median time-to-diagnosis was 17 days without IHC and 28 days for cases with IHC (Figure 1D).

The nature of treatment delay and its components in SSA have not been well described. This prospective multicenter study found that

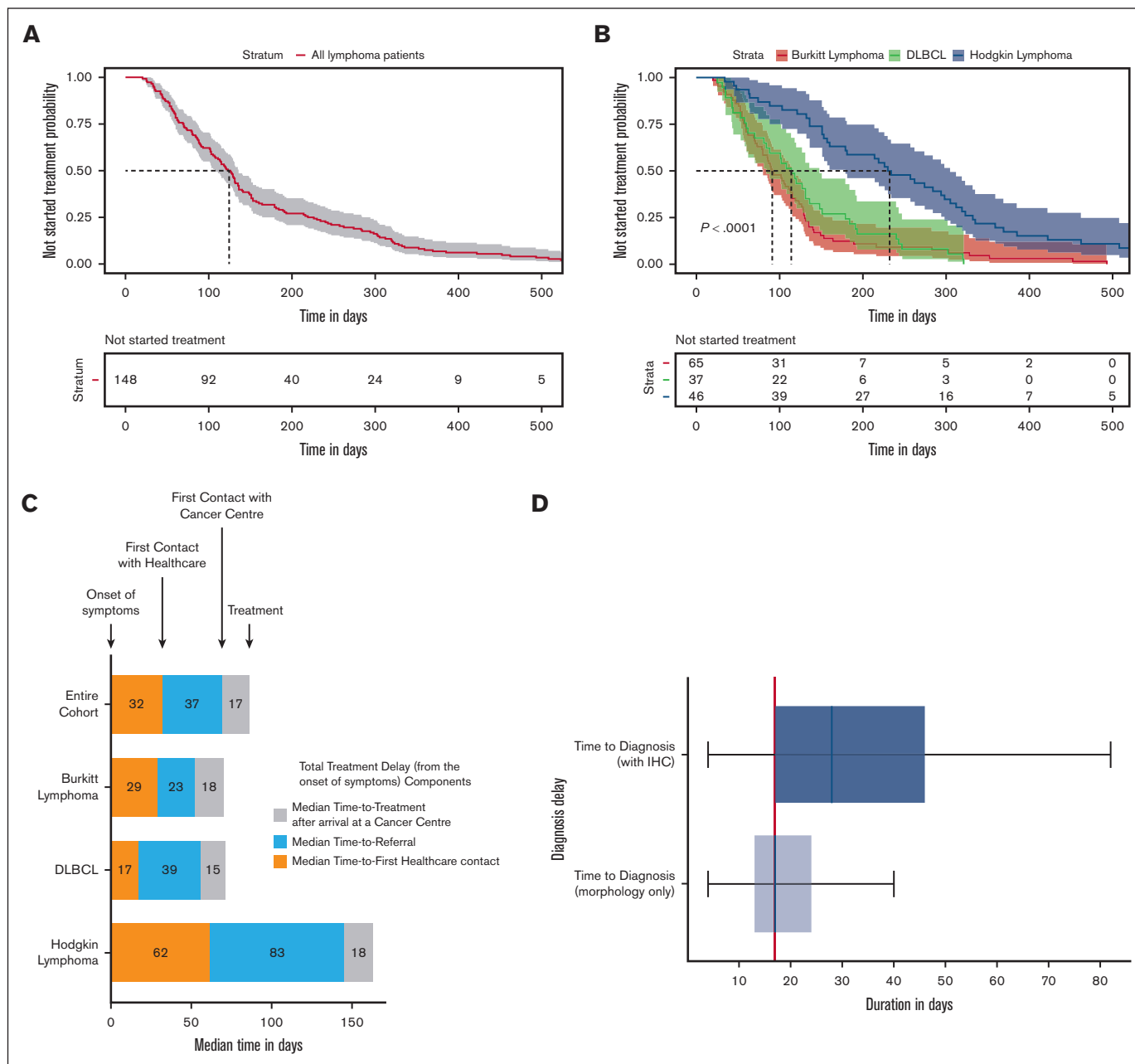


Figure 1. Total treatment delay (total time-to-treatment from the onset of symptoms) and diagnosis delay after arrival to cancer centers. (A) Total treatment delay across all lymphoma types and (B) for individual types of lymphoma. The shaded region shows 95% CIs. (C) Total treatment delay (from the onset of symptoms) components. (D) Boxplots of the time-to-diagnosis for morphology-only and IHC reports after the arrival to cancer centers for the entire cohort. The vertical red line indicates the median time-to-treatment after arrival at a cancer center (17 days).

patients presenting with signs of typical BL had a significantly shorter time-to-treatment (median, 91 days) compared with those with DLBCL (114 days) and HL (232 days). However, this delay is still far beyond the recommended time of 5 days for BL. We attribute these differences in total treatment delay between BL, DLBCL, and HL to the characteristic jaw mass presentation and rapid increase in tumor size seen among patients with BL, contrary to the presence of slowly progressive peripheral lymphadenopathy or mediastinal mass in patients with HL, which can be wrongly diagnosed as tuberculosis. In addition, BL is 1 of the region's most

studied childhood cancers, and there is awareness among the public and health care workers of the need for rapid referral.¹⁰ Importantly, health care-related delays (time-to-referral and time-to-treatment after arrival at the cancer center) make up two-thirds of the total treatment delay, with limited diagnostic capacity at primary-level facilities significantly contributing to the observed referral delay. Furthermore, we observed that the median time-to-treatment after arrival at the cancer center (17 days) corresponded to the time-to-diagnosis (morphology only), which was also 17 days. By contrast, the time to World Health Organization

gold standard diagnosis for lymphoma, the time-to-diagnosis (with IHC) was 28 days for the entire cohort. Importantly, the diagnosis had changed among 20.7% of patients after review of IHC (Table 1). These results show that even in a research setting where automated IHC was made available, treatment often had to be instituted based on morphological diagnosis alone because of a combination of long turnaround times for IHC and clinical urgency, thus increasing the risk of misdiagnosis.

In conclusion, significant treatment delays for patients with lymphoma emanate from health care system-related factors. Because of delays in referrals from primary care and a lack of capacity for pathology in secondary care, initial treatment decisions are often based on clinical suspicion, urgency, and morphology alone. New diagnostic approaches for BL that overcome these health care-related delays are urgently needed to improve the outcome of children with this highly curable disease.

The study received an institutional review board approval from the Oxford Tropical Research Ethics Committee (OxTREC reference, 15-19), National Institute of Medical Research (NIMR registration number NIMR/HQ/R.8a/Vol.IX/3408) in Tanzania, Uganda National Council of Science and Technology (UNCST registration number HS529ES), and the Lacor Hospital Institutional Research Ethics Committee (LHIREC number 074/05/19) in Uganda. Initial research ethics committee approval was given on 6 February 2019 (protocol version 3.1), and the current protocol version 3.3 was approved on 4 April 2021 via substantial amendment. Participants were enrolled in the study only after written informed consent or assent had been obtained from the patient as per the institutional review board guidelines.

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ORCID profiles: W.F.M., 0000-0002-0016-7551; L.M., 0000-0001-6382-1795; E.M., 0000-0001-5938-5628; C.C., 0000-0001-5154-7872; D.V., 0000-0002-3984-1507; A.S., 0000-0002-3938-8490.

Correspondence: William Frank Mawalla, Department of Haematology and Blood Transfusion, Muhimbili University of Health and Allied Science (MUHAS), PO Box 65001, Upanga, Dar es Salaam, Tanzania; email: mawallawf@gmail.com.

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