Clinical Characteristics and Histopathological Patterns of Hodgkin Lymphoma and Treatment Outcomes at a Tertiary Cancer Center in Ethiopia

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Purpose
In developing countries, Hodgkin lymphoma (HL) affects the young population. In Ethiopia, nearly 70% of the population are < 35 years of age. Therefore, this study aimed to elucidate the age distribution, histopathologic patterns, clinical characteristics and treatment outcomes of HL in Ethiopia.

Materials and Methods
Data from clinical records of 133 consecutive patients with HL between 2014 and 2019 were reviewed and collected. Formalin-fixed paraffin-embedded tissue blocks of HL cases were collected and used for subtype classification.

Results
A total of 68.4% (91) of the patients were male; male-to-female ratio was 2.2:1. The median age was 22 years. The age distribution was 57.1% (76), 30.8% (41), and 2.3% (3) for the age groups (10-29), (30-59), and (60-69) years, respectively. Thirteen percent (12) were associated with HIV. The majority of the cases, 50.4% (67), were of the mixed-cellularity (MCCHL) subtypes and 30% (40) nodular-sclerosis (NSCCHL). Most HIV-associated cases (60%, 6) were of the MCCHL subtype. The 4-year overall survival (OS) was 83.1%. The 4-year OS of early-stage patients was 100% and advanced-stage patients with low-risk (International Prognostic Score [IPS] ≤ 2) and high-risk (IPS ≥ 3) were 94.1% and 62.9%, respectively. All patients who received combined-therapy survived, whereas those who received doxorubicin, bleomycin, vinblastine, and dacarbazine only showed a 4-year OS rate of 77.9%.

Conclusion
HL affects the youngest and most productive population in Ethiopia. The treatment outcome is favorable in both HIV-associated and non–HIV-associated HL. However, the study population was likely a highly selected group as the majority of the Ethiopian population do not have access to specialized care.

INTRODUCTION
Hodgkin lymphoma (HL) is a distinctive lymphoid neoplasm with a characteristic clinical presentation, epidemiology, and histopathologic pattern.1 HL was the first lymphoid malignancy to be described, in 1832.2 HL affects all age groups, but is reported to be most common in age groups between 20 and 34 years.3 In high-income countries, the onset of HL shows a bimodal distribution. The first peak is observed in the age groups between 15 and 35 years, and a second incidence peak can be observed after the age of 50 years.4 In low-income countries, HL is among the most common cancers in adolescents and younger adults,5 and the second peak does not occur.5,7 In Ethiopia, 70% of the population are younger than 35 years of age.8,9

The global incidence of HL is about 3/100,000 per year.10 The 5-year prevalence for HL in the world, Africa, and Ethiopia is estimated to be (3.6)/100,000, (2.0)/100,000, and (1.5)/100,000, respectively. The estimated mortality rate is (0.30), (0.48), and (0.40) for the world, Africa, and Ethiopia, respectively.11 Studies conducted to assess the pattern of cancer in Ethiopia have shown a considerable number of patients diagnosed with HL.7 Recent estimates indicated that hematologic malignancies comprise the third leading cause of cancer and cancer-related mortality in Ethiopia, of which nearly 20% are HL.7,12

HL has a unique histomorphologic presentation with a minority of neoplastic cells, which comprise < 1% of the total cell population, and a large majority of nonmalignant reactive immune cells.13 HL has been divided into two major types: classical HL,14 which accounts for 90% of all cases, and nodular lymphocyte-predominant HL (NLPHL) depending on morphologic, phenotypic, genotypic, and clinical findings.15 The classical Hodgkin lymphoma (CHL) is further subtyped into nodular sclerosis CHL (NSCHL), lymphocyte-rich CHL (LRCHL), mixed-cellularity CHL (MCCHL), and lymphocyte-depleted CHL (LDCHL).
subtypes. In high- and middle-income countries, the predominant subtype is NSCHL, whereas in low-income countries, MCCHL and LDCHL subtypes are predominant. The incidence of HL has increased in sub-Saharan Africa during the burden of HIV. Probably, HIV increases the risk of HL because of loss of immunity. The majority of HL cases associated with HIV are of MCCHL and LDCHL subtypes.

Ethiopia is one of the sub-Saharan African countries in which cancer is becoming one of the major public health problems. Tikur Anbessa Specialized Hospital (TASH) is the only cancer treatment center in the country. All cancer patients seeking diagnosis and treatment are referred to this hospital. Unfortunately, not all patients can afford the cost of traveling and treatment. In addition, the absence of a cancer registry throughout the country except for the recently launched one by the Addis Ababa city administration contributes to the low estimation of cancer incidence and mortality rate in the country. Thus, it is very difficult to estimate the real picture of incidence and mortality rate of HL. This study is designated to elucidate age distribution, clinical characteristics, histopathologic subtypes, and survival outcome of HL in an Ethiopian setting.

**MATERIALS AND METHODS**

This is a retrospective study of HL cases diagnosed at TASH during the period 2014-2019. The clinical records of 133 HL cases were reviewed, from which demographic data, histopathologic subtypes of HL, stage of the disease, and other related clinical data were collected. At TASH, staging of patients with HL includes detailed history with special attention to the presence or absence and duration of systemic (B) symptoms and pruritus; adequate surgical biopsy; physical examination with particular emphasis to lymph node regions and organs; complete blood count and differential erythrocyte sedimentation rate; plain chest x-rays with measurement of mediastinal mass; abdominal ultrasonographic studies; computed tomography scan of the neck, chest, abdomen, and pelvis; and bone marrow aspiration and biopsy for stage IV disease, and stage III if the patient has cytopneas. Since there is no electronic cancer or death registry system, patients whose records lacked follow-up data were contacted through their cellphone numbers that were available on the clinical records. Accordingly, 71 of 133 HL cases were included for the overall survival (OS) analysis.

Formalin-fixed paraffin-embedded tissue blocks of the HL cases were collected from the archives of the pathology department of TASH. The tissue blocks were used for classification of HL into CHL and NLPHL subtypes. Cases were reviewed by a specialist in hematopathology (A.K.) and reassessed according to 2016 WHO classification of Tumors of Hematopoietic and Lymphoid Tissues. Two whole sections with 3-4-µm thickness were prepared from each tissue block and stained with hematoxylin and eosin and CD30. A tissue microarray (TMA) was constructed from the collected formalin-fixed paraffin-embedded tissue blocks, a method validated also in HL.

| Table 1. Primary Antibody Characteristics |
|-----------------|-------------|----------|-------------|-----------------|
| Antigen | Clone | Dilution | Supplier | Antigen-Retrieval Method |
|--------|-------|----------|-----------|-------------------------|
| CD30   | Ber-H2 | 1:50     | Agilent/DAKO | PT-Link pH9             |
| CD15   | Carb-3 | 1:50     | Agilent/DAKO | PT-Link pH9             |
| PAX5   | SP34  | 1:200    | Cell Marque | PT-Link                |
| CD20cy | L26   | 1:500    | Agilent/DAKO | PT-Link pH9             |
| CD3    | A0452 | 1:200    | Agilent/DAKO | PT-Link pH9             |
| CD79a  | JCB117 | 1:500   | Agilent/DAKO | PT-Link pH9             |
| CD45   | 2B11 + PD7/26 | 1:300 | Agilent/DAKO | PT-Link pH9             |
| CD57   | TB01  | 1:100    | Agilent/DAKO | PT-Link pH9             |
| OCT-2  | EPR16570 | 1:1,000 | Abcam       | PT-Link pH9             |
| PD-1   | NATI05 | 1:100    | Cell Marque | 2100 Retriever pH6        |
Slides with TMA sections were stained with the following antibodies (Abs): CD30, CD15, PAX5, CD20, CD79a, CD45, OCT-2, PD-1 and CD57, and CD3 to characterize and subclassify HL. PD-1 and CD57 markers were used for the differential diagnosis of NLPHL, CHL, and T-cell histocyte-rich large B-cell lymphoma.26 The whole and TMA sections were dewaxed, deparaffinized, and antigen-retrieved either in high pH or in low pH.27 Polymer-based immunohistochemistry techniques were used to stain the TMA and tissue sections with the Abs.28 Details of the primary antibodies and dilutions are shown in Table 1. Descriptive statistics were used to explore the demographic characteristics, clinical variables of HL cases, and treatment modalities. Chi-square test or Fisher’s exact test was used to show the differences and distributions of different variables. OS of HL cases in the study was calculated by using the date of diagnosis and time of last date of the patients known to be alive, date of death, or last date of follow-up, and estimated according to the Kaplan-Meier method. Mann-Whitney U and Kruskal-Wallis tests were used to analyze the distribution of age among nominal and categorical variables, respectively. Analysis of variance or univariate analysis was used to show the mean differences of age among the groups of categorical variables. A result with \( P \) value < .05 was considered statistically significant.

Ethical clearance was obtained from Addis Ababa University College of Natural Sciences, College of Health Sciences Institutional Ethics review boards, and Ethical Review board of Armauer Hansen Research Institute in accordance with the Declaration of Helsinki.

RESULTS

Out of a total of 133 patients with HL, 68.4% (91) were males and 31.6% (42) females, with a male-to-female ratio of 2.2:1 and a \( P \) value of < .001 (Table 2). The patients’ age ranged between 4 and 66 years, with a median age of 22 years. The most affected age groups in this study were adolescent (10-19 years) and young adults (20-29 years) that accounted for 33.1% (43) and 24.6% (32) of the total number, respectively. The elderly (≥ 60 years) represented only 2.3% (3) of the cases (Appendix Fig A1). There was no significant difference in age distribution between male and female patients. The majority of patients were from Oromia Regional State 35.2% (43), followed by Addis Ababa 27.9% (34) and Amhara Regional State 22.1% (27), as depicted in Appendix Table A1.

Most of the patients 54.9% (73) presented with one or more of the B-symptoms at diagnosis. According to the Ann Arbor staging system,29 26.5% (31), 39.3% (46), 21.4% (25), and 12.8% (15) of the patients, respectively, presented with stage I, II, III, and IV at diagnosis. 65.1% (84) of the patients presented with anemia. Hemoglobin levels of < 13.7 g/dL for males and < 11.2 g/dL for females were used to diagnose anemia; 61.8% (81) of the patients presented with lymphocytopenia (cutoff < 1.18 × 10^3/L)
and 54.2% (71) with monocytopenia (cutoff < 0.24 x 10^3/µL). MCCHL was the dominant histopathologic subtype 50.4% (67) followed by NSCHL 30.1% (40), as displayed in Table 2. The MCCHL subtype was more common in males 72.1% (44) than in females 27.9% (17), with a ratio of 2.6:1. The distribution of NSCHL subtype among sexes was almost similar, with a ratio of 1.2:1 as depicted in Appendix Table A2. The median age of HL cases was different between the CHL subtype and the NLPHL, 21 and 38 years, respectively, (P = .004). MCCHL and NSCHL were more common among patients up to 29 years of age, whereas NLPHL was more common among patients older than 30 years of age (Appendix Fig A2).

HIV results were available for 92 patients, and 13% (12) were positive. 63.7% (7) of these presented with stage I-II at diagnosis. However, 75% (9) of HIV-positive cases were categorized into the group of advanced stage when restaged using B-symptoms. The distribution of HIV-associated HL was similar between males and females in this study. 83.3% (10) of HIV-associated HL cases were within the age group of > 14 years. 60% (6) of HIV-associated HL cases were of the MCCHL subtype followed by NSCHL subtype (3, 30%), as demonstrated in Table 3. Monocytopenia was strongly associated with HIV, 75% (9) of HIV-associated HL had low monocyte counts.

The majority of patients 93.4% (124) were treated with the standard chemotherapy regimen doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD), whereas 6.8% (9) of the patients, all belonging to the pediatric population, were treated with ABVD followed by cyclophosphamide, vincristine sulfate, prednisone, and dacarbazine (COPDAC). 3.8% (5) of the patients received ABVD and COPDAC followed by radiotherapy, and only 0.8% (1) was treated with ABVD followed by radiotherapy. The number of ABVD treatment cycles in this study ranged between 4 and 8 cycles. Three patients (2.3%) received < 4 cycles of ABVD; these patients stopped treatment and follow-up earlier than planned. The number of COPDAC cycles ranged between 2 and 6 cycles. 48.3% (14) of patients with HL within the age group ≤ 14 years were treated with the ABVD regimen only, whereas 51.7% (15) of this age group were treated with combined chemotherapy and of these patients, five had additional radiotherapy. All HL cases within the age group > 14 years were treated with ABVD. A total of 94.7% (36) patient cases with early stage disease received ABVD only, one received combined chemotherapy, and one received combined chemotherapy with radiotherapy. 85.1% (74) and 14.9% (13) of HL cases with advanced-stage disease received ABVD only or combined chemotherapy with or without radiotherapy respectively.

The comparison between patients with complete (71/53.4%) and incomplete follow-up data (62/46.6%) revealed that the distribution of age between these two groups was significantly different (P = .001), with median ages of 17 and 25 years, respectively. No significant differences were found in the distribution of sex, stage, WBC and lymphocyte count, IPS (International Prognostic Score), or HL subtype. However, the group with complete survival data presented with lower hemoglobin, higher monocyte count, and was less frequently associated with HIV.

The 4-year OS for patients in this study was 83.1% (Fig 1), with a 19-month median follow-up time. The 4-year OS of patients with early-stage and advanced-stage disease was 100% and 78.2%, respectively. Patients presenting with stage I, II, III, and IV had 4-year OS rates of 94.1%, 76.3%,
TABLE 3. Demographic and Clinical Characteristics of Patients With HL According to HIV Status

| Clinical Characteristics | HIV-Positive No. (%) | HIV-Negative No. (%) | 95% CI | P     |
|--------------------------|----------------------|----------------------|--------|-------|
| HL subtypes              |                      |                      |        |       |
| MCCHL                    | 6 (12)               | 44 (88)              |        | .219  |
| NSCHL                    | 3 (10)               | 27 (90)              |        |       |
| LRCHL                    | 2 (50)               | 2 (50)               |        |       |
| LDCHL                    | 0                    | 2 (100)              |        |       |
| NLPHL                    | 1 (20)               | 4 (80)               |        |       |
| Stage of the disease     |                      |                      |        | .485  |
| Stage I                  | 4 (15.4)             | 22 (84.6)            |        |       |
| Stage II                 | 3 (12)               | 22 (88)              |        |       |
| Stage III                | 1 (5.3)              | 18 (94.7)            |        |       |
| Stage IV                 | 3 (23.1)             | 10 (76.9)            |        |       |
| Early stage              | 3 (12.5)             | 21 (87.5)            |        |       |
| Advance stage            | 9 (13.4)             | 58 (86.6)            |        |       |
| Sex distribution         |                      |                      |        |       |
| Male                     | 6 (9.5)              | 57 (90.5)            |        |       |
| Female                   | 6 (22.2)             | 21 (77.8)            |        |       |
| Age groups               |                      |                      |        |       |
| ≤ 14 years               | 2 (7.1)              | 26 (92.9)            |        |       |
| > 14 years               | 10 (15.9)            | 53 (84.1)            |        |       |
| WBC count × 10^3/µL      |                      |                      |        |       |
| ≥ 3.98                   | 7 (8.8)              | 73 (91.3)            | 0.07   | 0.67  |
| < 3.98                   | 5 (45.5)             | 6 (54.5)             |        | .005  |
| Lymphocyte count × 10^3/µL |                    |                      |        |       |
| ≥ 1.18                   | 3 (6.7)              | 42 (93.3)            | -0.007 | 0.26  |
| < 1.18                   | 9 (19.6)             | 37 (80.4)            |        | .069  |
| Monocyte count × 10^3/µL  |                      |                      |        |       |
| ≥ 0.24                   | 3 (5.6)              | 51 (94.4)            | 0.04   | 0.34  |
| < 0.24                   | 9 (24.3)             | 28 (75.7)            |        | .013  |
| Hemoglobin, g/dL         |                      |                      |        |       |
| ≥ 11.2                   | 5 (17.2)             | 24 (82.8)            | -0.22  | 0.10  |
| < 11.2                   | 7 (11.5)             | 54 (88.5)            |        | .51   |

Abbreviations: HL, Hodgkin lymphoma; CHL, classical Hodgkin lymphoma; LDCHL, lymphocyte-depleted CHL; LRCHL, lymphocyte-rich CHL; MCCHL, mixed-cellularity CHL; NLPHL, nodular lymphocyte-predominant HL; NSCHL, nodular sclerosis CHL.

Several risk factors have been related to HL such as sex, age, race, and genetic and environmental factors. Male sex has been stated as a risk factor for contracting HL. By contrast, our study showed more cases among the younger age group, and was rare among the elderly. This is partly explained by the differences in demographic distribution, which is characterized by large proportion of younger age group and consequently, HL significantly decreased after the age of 50 years. Our finding is similar to what reported from other low-income countries.

DISCUSSION

HL has shown differences in age distribution and histopathologic subtypes in different geographical, genetic, and environmental settings. In high-income countries, HL shows a bimodal age distribution at diagnosis. By contrast, our study showed more cases among the younger age group, and was rare among the elderly. This is partly explained by the differences in demographic distribution, which is characterized by large proportion of younger age group and consequently, HL significantly decreased after the age of 50 years. Our finding is similar to what reported from other low-income countries.

The majority of HL cases in this study (65.8%) were categorized as stage I and II at diagnosis. This is in contrast to a study conducted in Nigeria, which reported a predominance of late stages. Furthermore, our finding showed that 63.7% of patients with HIV-associated HL presented with early stages at diagnosis. This is consistent with a study reporting that patients with HIV were more likely to present at early stages of any type of cancer compared with the general population in Africa. In HL, the hemoglobin level and peripheral WBC count and composition are important prognostic factors at diagnosis and at treatment evaluation, and are part of the IPS for
patients with advanced-stage disease. In this study, 65.1% of HL cases presented with low hemoglobin and most WBC compositions also were low in the majority of cases. Similarly, 53% of patients with HL were found to be anemic in a study conducted in Pakistan.39

The dominant HL subtypes in this study was MCCHL (50.4%), consistent with findings from Kenya (44.9%) and lower than reported from Nigeria (64.3%).40 However, the second dominant subtype was NSCHL in our study, which is different from the finding from Kenya and Nigeria, in which NLPHL was the second dominant subtype.5,6 By contrast, a recent study from Egypt has reported NSCHL as a common subtype of HL.32 Previous studies from the United States and Europe indicate the NSCHL subtype to be the dominant subtype.34,46 This discrepancy might be because of differences on environmental factors and exposure to infections.17,41 Most HIV-positive HL cases were MCCHL subtypes followed by NSCHL. Our finding is similar to the report of a study from South Africa.42 Several reports suggest the possible association of MCCHL subtype of HL with viral infection, especially of Epstein-Barr Virus.18,41

To our knowledge, this is the first study conducted to evaluate survival and prognostic factors of patients with HL in Ethiopia. The 4-year OS was estimated to be 83.1%, although median time of follow-up was relatively short, 19 months. This is similar to that reported from Malawi, with a 1-year OS rate of 83%.43 and Nigeria, which reported an OS rate of 84.3%.44 A study from Turkey reported a 10-year OS of 84%,45 and others from the United States and the Nordic countries reported a 5-year relative survival ratio of 80%.34,46 In Ethiopia, the standard first-line treatment regimen for HL is ABVD. However, the 4-year OS of patients who received ABVD only was 77.9%, a result which is similar to what was reported by Santoro et al,67 but lower than reported in other populations (88%-90%).45,48 By contrast, the group of patients with HL that received combined chemotherapy only or received combined chemotherapy followed by radiotherapy showed an excellent outcome in this study.

In this study, we were able to confirm the prognostic impact of the IPS. In our series, however, the strongest prognostic factor was lymphocytopenia. Generally, MCCHL and LDCHL are considered to be the HL subtypes associated with worst survival outcome, and NLPHL subtype has a good prognosis and survival outcome.49 In this study, the impact of histopathologic subtype could partly be confirmed. LDCHL was associated with the most inferior outcome, followed by MCCHL and NSCHL, but all patients with NLPHL were long-term survivors.

Our study has several limitations. It is a hospital-based retrospective study and the sample size was relatively small, which may affect the strength of the findings. As the study included only cases who attended or were referred to TASH during the study period, bias issues concerning the number of patients who are treated at TASH compared with the patients who did not get access for diagnosis and treatment may be raised. Another limitation of the study was the lack of an organized cancer and death registry system in Ethiopia, which may underestimate the rate of disease progression and lymphoma-related deaths. The median follow-up time is also short, <2 years.

In conclusion, the populations at risk for HL in Ethiopia are adolescent and young adults, and the risk of HL declined gradually in older ages. In general, the treatment outcome for the patients included in this series was favorable and comparable to that of other populations, including in HIV-infected individuals. Our results showed that even in a low-resource setting, excellent treatment outcomes can be achieved after appropriate diagnostic workup and standard chemotherapy. The majority of HL
# TABLE 4. OS and Prognostic Factors

| Characteristics       | 1-Year OS% | 2-Year OS% | 3-Year OS% | 4-Year OS% | P     |
|-----------------------|-----------|-----------|-----------|-----------|-------|
| OS                    | 97.0      | 90.0      | 83.1      | 83.1      |       |
| IPS                   |           |           |           |           | .177  |
| IPS ≤ 2               | 100       | 93.3      | 93.3      | 93.3      |       |
| IPS ≥ 3               | 96.3      | 86.2      | 68.9      | 68.9      |       |
| Sex                   |           |           |           |           | .746  |
| Male                  | 97.4      | 91.2      | 80.5      | 80.5      |       |
| Female                | 96.0      | 87.3      | 87.3      | 87.3      |       |
| Age group             |           |           |           |           | .4    |
| 0-9                   | 91.7      | 91.7      | 91.7      | 91.7      |       |
| 10-19                 | 94.1      | 83.7      | 83.7      | 83.7      |       |
| 20-29                 | 92.9      | 74.3      | 49.5      | 49.5      |       |
| > 30                  | 100       | 90        | 90        | 90        |       |
| Ann Arbor staging     |           |           |           |           | .654  |
| Stage I               | 94.1      | 94.1      | 94.1      | 94.1      |       |
| Stage II              | 94.1      | 76.3      | 76.3      | 76.3      |       |
| Stage III             | —         | 90.9      | 75.8      | 75.8      |       |
| Stage IV              | —         | —         | 66.7      | 66.7      |       |
| Early and advanced stages |       |           |           |           |       |
| (Stage I and IIA) early stage | 100 |       |           |           | .140  |
| Advanced stage (stage I and II, III, and IV) | 96.1 | 87.4 | 78.2 | 78.2 |       |
| HL subtypes           |           |           |           |           | .721  |
| MCCHL                 | 96.2      | 86.5      | 86.5      | 86.5      |       |
| NSCHL                 | 96.3      | 89.9      | 89.9      | 89.9      |       |
| LDCHL                 | 100       | 50        | —         | —         |       |
| LRCHL                 | —         | —         | —         | —         |       |
| NLPHL                 | 100       | —         | —         | —         |       |
| WBC count             |           |           |           |           | .069  |
| WBC > 10.04 × 10^9/µL | 95.4      | 92.6      | 85.3      | 76.3      |       |
| WBC ≤ 10.04 × 10^9/µL | 100       | 100       | 100       | 100       |       |
| Lymphocyte x 10^3/µL  |           |           |           |           | .015  |
| > 600                 | 100       | 100       | 100       | 100       |       |
| ≤ 600                 | 94.3      | 82.6      | 70.8      | 70.8      |       |
| Monocyte x 10^3/µL    |           |           |           |           | .078  |
| > 0.24                | 100       | 94.7      | 88.8      | 88.8      |       |
| < 0.24                | 91.8      | 82.8      | 74.5      | 74.5      |       |
| Hemoglobin, g/dL      |           |           |           |           | .772  |
| ≥ 10.5                | 100       | 91.7      | 91.7      | 91.7      |       |
| < 10.5                | 97.7      | 91.4      | 83.1      | 83.1      |       |
| Treatment             |           |           |           |           | .112  |
| ABVD only             | 77.9      |           |           |           |       |
| ABVD plus             | 100       |           |           |           |       |

Abbreviations: ABVD plus, patients treated with combined chemotherapy ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) and COPDAC (cyclophosphamide, vincristine sulfate, prednisone, and dacarbazine) or radiotherapy; CHL, classical Hodgkin lymphoma; HL, Hodgkin lymphoma; IPS, International Prognostic Score; LDCHL, lymphocyte-depleted CHL; LRCHL, lymphocyte-rich CHL; MCCHL, mixed-cellularity CHL; NLPHL, nodular lymphocyte-predominant HL; NSCHL, nodular sclerosis CHL; OS, overall survival.
cases in this study were from regions near to Addis Ababa, and very few from more distant regions, indicating that most of the population of the country were not able to get access to cancer medical services, which is the main obstacle for improving the outcome for patients with HL in Ethiopia.

REFERENCES
1. Mwakigonja AR, Kaaya EE, Heiden T, et al: Tanzanian malignant lymphomas: WHO classification, presentation, ploidy, proliferation and HIV/EBV association. BMC Cancer 10:344, 2010
2. Hodgkin T: On some morbid appearances of the absorbent glands and spleen. Med Chir Soc Trans 17:68-114, 1832
3. Shanbhag S, Ambinder RF: Hodgkin lymphoma: A review and update on recent progress. CA Cancer J Clin 68:116-132, 2018
4. Thomas R, Re D, Zander T, et al: Epidemiology and etiology of Hodgkin disease by in situ hybridization with biotinylated probes on specially processed modiﬁed acetone methyl benzoate xylene (ModAMeX) sections. Blood 77:1781-1786, 1991
5. Aldinucci D, Gloghini A, Pinto A, et al: The classical Hodgkin lymphoma microenvironment and its role in promoting tumour growth and immune escape. J Pathol 221:248-263, 2010
6. Riyat MS: Hodgkin’s disease in Kenya. Cancer 69:1047-1051, 1992
7. Tefera B, Assefa M, Abebe B, et al: Patterns of cancer in University of Gondar Hospital: North-West Ethiopia. J Oncol Med Pract 1:2, 2016
8. www.cia.gov/CIA: Central Intelligence Agency, The World Factbook.: Africa: Ethiopia, 2020
9. CSA: Population and Housing Census of Ethiopia 2007: Statistical Report. International Household Survey Network (IHSN), Addis Ababa, Ethiopia, Federal Democratic Republic of Ethiopia, 2007
10. TorreLA, Bray F, Siegel RL, et al: Global cancer statistics, 2012. CA Cancer J Clin 65:87-108, 2015
11. IARC: Cancer Today (powered by GLOBOCAN 2018). IARC Cancer Base No. 15. Ed. Ferlay J, Ervik M, Lam F, et al. Lyon, France, IARC, 2020
12. Woldeamanuel YW, Girma B, Teklu AM: Cancer in Ethiopia. Lancet Oncol 14:289-290, 2013
13. Aldinucci D, Gioglini A, Pinto A, et al: The classical Hodgkin’s lymphoma microenvironment and its role in promoting tumour growth and immune escape. J Pathol 221:248-263, 2010
14. Brousset P, Chittal S, Schlaffer D, et al: Detection of Epstein-Barr virus messenger RNA in Reed-Sternberg cells of Hodgkin’s disease by in situ hybridization with biotinylated probes on specially processed modified acetone methyl benzoate xylene (ModAMeX) sections. Blood 77:1781-1786, 1991
15. Harris NL, Jaffe ES, Stein H, et al: A revised European-American classification of lymphoid neoplasms: A proposal from the International Lymphoma Study Group. Blood 84:1361-1392, 1994
16. Swerdlow SH, Campo E, Pileri SA, et al: The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood 127:2375-2390, 2016

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
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DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
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AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
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17. Belkaid M, Briegre J, Djebbara Z, et al: Comparison of Epstein-Barr virus markers in Reed-Sternberg cells in adult Hodgkin’s disease tissues from an industrialized and a developing country. Leuk Lymphoma 17:163-168, 1995
18. Leoncini L, Spina D, Nyong’o A, et al: Neoplastic cells of Hodgkin’s disease show differences in EBV expression between Kenya and Italy. Int J Cancer 65:781-784, 1996
19. Kusuda M, Toriyama K, Kamidigo NO, et al: A comparison of epidemiologic, histologic, and virologic studies on Hodgkin’s disease in western Kenya and Nagasaki, Japan. Am J Trop Med Hyg 59:801-807, 1998
20. Casper C: The increasing burden of HIV-associated malignancies in resource-limited regions. Annu Rev Med 62:157-170, 2011
21. Bohtius J, Schmidlin K, Boue F, et al: HIV-1-related Hodgkin lymphoma in the era of combination antiretroviral therapy: Incidence and evolution of CD4(+) T-cell lymphocytoses. Blood 117:6100-6108, 2011
22. Grewal R, Irmie A, Nadoor N, et al: Hodgkin’s lymphoma and its association with EBV and HIV infection. Crit Rev Clin Lab Sci 55:102-114, 2018
23. Kononen T, Huhandorf L, Kallioniemi A, et al: Tissue microarrays for high-throughput molecular profiling of tumor specimens. Nat Med 4:844-847, 1998
24. Tzankov A, Zimpfer A, Pehrs A-C, et al: Expression of B-cell markers in classical Hodgkin lymphoma: A tissue microarray analysis of 330 cases. Mod Pathol 16:1141-1147, 2003
25. Hedvat CV, Hegde A, Chaganti RS, et al: Application of tissue microarray technology to the study of non-Hodgkin’s and Hodgkin’s lymphoma. Hum Pathol 33:968-974, 2002
26. Stein HPS, Weiss LM, Poppema S, et al: Hodgkin lymphomas, in Swerdlow SHCE, Harris NL, Jaffe ES, et al (eds): WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues (ed 4). Lyon, France, IARC, 2017, pp 423-441
27. Kim SH, Kook MC, Shin YK, et al: Evaluation of antigen retrieval buffer systems. J Mol Histol 35:409-416, 2004
28. Cordell JL, Falini B, Erber WN, et al: Immunoenzymatic labeling of monoclonal antibodies using immune complexes of alkaline phosphatase and monoclonal anti-alkaline phosphatase (APAAP complexes). J Histochem Cytochem 32:219-229, 1984
29. Carbone PP, Kaplan HS, Musshoff K, et al: Report of the Committee on Hodgkin’s Disease Staging Classification. Cancer Res 31:1860-1861, 1971
30. Saarinen S, Pukkala E, Vahteristo P, et al: High familial risk in nodular lymphocyte-predominant Hodgkin lymphoma. J Clin Oncol 31:938-943, 2013
31. Cozen W, Katz J, Mack TM: Risk patterns of Hodgkin disease in Los Angeles vary by cell type. Cancer Epidemiol Prev Biomarkers 1:261-268, 1992
32. Zeggai S, Harir N, Belkacem A, et al: Clinical-pathological features and histological variants of Hodgkin’s lymphoma: A study of 526 patients. Egypt J Haematol 41:140, 2016
33. Carterwright RA, Gunney KA, Moorman AV: Sex ratios and the risks of hematological malignancies. Br J Haematol 118:1071-1077, 2002
34. Shenoy P, Maggioncalda A, Malik N, et al: Incidence patterns and outcomes for Hodgkin lymphoma patients in the United States. Adv Hematol 2011:725219, 2011
35. Motawy MS, Omar YT: Hodgkin’s disease in children in Kuwait. Cancer 57:2255-2259, 1986
36. Goedert JJ, Coté TR, Virgo P, et al: Spectrum of AIDS-associated malignant disorders. The Lancet 351:1833-1839, 1998
37. Menon MP, Coghill A, Mutyaba IO, et al: Association between HIV infection and cancer stage at presentation at the Uganda Cancer Institute. J Glob Oncol 4:1-9, 2018
38. Shiel MS, Koritzinsky EH, Clarke CA, et al: Prevalence of HIV Infection among U.S. Hodgkin lymphoma cases. Cancer Epidemiol Biomarkers Prev 23:274-281, 2014
39. Yasmeen T, Ali J, Khan K, et al: Frequency and causes of anemia in lymphoma patients. Pak J Med Sci 35:61-65, 2019
40. Raperazzi D, Ugolini D, Ferraris AM, et al: Histological subtypes of Hodgkin’s disease in the setting of HIV infection. Ann Hematol 80:340-344, 2001
41. Glaser SL, Lin RJ, Stewart SL, et al: Epstein-Barr virus-associated Hodgkin’s disease: Epidemiologic characteristics in international data. Int J Cancer 70:375-382, 1997
42. Patel M, Philip V, Fazel F: Human immunodeficiency virus infection and Hodgkin’s lymphoma in South Africa: An emerging problem. Adv Hematol 2011:578163, 2011
43. Stanley CC, Westmoreland KD, Itimu S, et al: Quantifying bias in survival estimates resulting from loss to follow-up among children with lymphoma in Malawi. Pediatr Blood Cancer 64: doi:10.1002/pbc.26370, 2017
44. Egesie OJ, Agaba PA, Silas OA, et al: Presentation and survival in patients with hematologic malignancies in Jos, Nigeria: A retrospective cohort analysis. J Med Trop 20:49-56, 2018
45. Kılıçkap S, Barışta İ, Üğer Ş, et al: Clinical features and prognostic factors of Hodgkin’s lymphoma: A single center experience. Balkan Med J 30:178, 2013
46. Storm HH, Klint A, Tryggvadottir L, et al: Trends in the survival of patients diagnosed with malignant neoplasms of lymphoid, hematopoietic, and related tissue in the Nordic countries 1964-2003 followed up to the end of 2016. Acta Oncol 49:694-712, 2010
47. 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. J Clin Oncol 5:27-37, 1987
48. Moccia AA, Donaldson J, Chhanabhai M, et al: International Prognostic Score in advanced-stage Hodgkin’s lymphoma: Altered utility in the modern era. J Clin Oncol 30:3383-3388, 2012
49. Bröckelmann PJ, Angelopoulou MK, Vassilakopoulos TP: Prognostic factors in Hodgkin lymphoma. Semin Hematol 53:155-164, 2016
APPENDIX

FIG A1. Age and sex distribution of patients with Hodgkin lymphoma during the study period.

FIG A2. HL subtypes among different age groups during the study period. CHL, classical Hodgkin lymphoma; HL, Hodgkin lymphoma; LDCHL, lymphocyte-depleted CHL; LRCHL, lymphocyte-rich CHL; MCCHL, mixed-cellularity CHL; NLPHL, nodular lymphocyte-predominant HL; NSCHL, nodular sclerosis CHL.
**FIG A3.** Overall survival of patients with HL at different stages of the disease. The 4-year OS was 94.1%, 76.3%, 75.8%, and 66.7% for stage I, stage II, stage III, and stage IV, respectively. HL, Hodgkin lymphoma.

**FIG A4.** Four-year overall survival of patients with HL who received different treatment regimens. The 4-year OS was 77.9% and 100% for patients received ABVD only and those received ABVD and COPDAC/radiotherapy (ABVD Plus), respectively. ABVD plus, patients treated with combined chemotherapy ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) and COPDAC (cyclophosphamide, vincristine sulfate, prednisone, and dacarbazine) with or without radiotherapy; HL, Hodgkin lymphoma.
### TABLE A1. Distribution of Patients With HL in Ethiopia During the Study Period

| Permanent Residence | No. | %     | Population     |
|---------------------|-----|-------|----------------|
| Addis Ababa         | 34  | 27.9  | 3,434,000      |
| Amhara              | 27  | 22.1  | 21,134,988     |
| Dire Dawa           | 1   | 0.8   |                |
| Harari              | 1   | 0.8   | 246,000        |
| Oromia              | 43  | 35.2  | 35,467,000     |
| SNPPR               | 12  | 9.8   | 19,170,007     |
| Somali              | 1   | 0.8   | 5,748,998      |
| Tigray              | 3   | 2.5   | 5,247,005      |
| Total               | 122 | 100.0 |                |

Abbreviations: HL, Hodgkin lymphoma; SNPPR, South Nations Nationalities and Peoples of Ethiopia region.

### TABLE A2. Proportion of Hodgkin Lymphoma Subtypes Among Sex and Age Groups

|                  | MCCHL | NSCHL | LRCHL | LDCHL | NLPHEL |
|------------------|-------|-------|-------|-------|--------|
|                  | No.   | %     | No.   | %     | No.    | %     | No. | %     | No. | %     |
| **Sex**          |       |       |       |       |        |       |     |       |     |       |
| Male             | 49    | 73.1  | 23    | 57.5  | 6      | 85.7  | 4   | 66.7  | 9   | 69.2  |
| Female           | 18    | 26.9  | 17    | 42.5  | 1      | 14.3  | 2   | 33.3  | 4   | 30.8  |
| M:F ratio        | 2.6:1 | 1.2:1 | 6:0   | 2:1   | 2:1    |       |     |       |     |       |
| **Age group**    |       |       |       |       |        |       |     |       |     |       |
| 0-9              | 9     | 13.4  | 3     | 7.5   | 0      | 0.0   | 1   | 16.7  | 0   | 0     |
| 10-19            | 26    | 38.8  | 12    | 30    | 3      | 42.9  | 0   | 0     | 2   | 15.4  |
| 20-29            | 16    | 23.9  | 11    | 27.5  | 1      | 14.3  | 4   | 66.7  | 1   | 7.3   |
| 30-39            | 7     | 10.4  | 6     | 15    | 1      | 14.3  | 1   | 16.7  | 4   | 30.8  |
| 40-49            | 3     | 4.5   | 2     | 5     | 2      | 28.6  | 0   | 0     | 3   | 23.1  |
| 50-59            | 5     | 7.5   | 4     | 10    | 0      | 0.0   | 0   | 0     | 3   | 23.1  |
| 60-69            | 1     | 1.5   | 2     | 5     | 0      | 0.0   | 0   | 0     | 0   | 0     |

Abbreviations: CHL, classical Hodgkin lymphoma; HL, Hodgkin lymphoma; LDCHL, lymphocyte-depleted CHL; LRCHL, lymphocyte-rich CHL; MCCHL, mixed-cellularity CHL; NLPHEL, nodular lymphocyte-predominant HL; NSCHL, nodular sclerosis CHL.