Epidemiological and clinical profiles of cutaneous leishmaniasis cases in Amhara National Regional State, Northwest Ethiopia: a multicenter retrospective study

Bizuayehu Gashaw,[1,2] Endalew Yizengaw,[3,4] Endalkachew Nibret,[2,4] Addisu Workineh,[1] Adisu Abebe[1]

[1]Amhara National Regional State Health Bureau, Bahir Dar; [2]Department of Biology, College of Science, Bahir Dar University; [3]Department of Medical Laboratory Science, College of Medicine and Health Science, Bahir Dar University; [4]Institute of Biotechnology, Bahir Dar University, Ethiopia

Correspondence: Endalew Yizengaw, Department of Medical Laboratory Science, Bahir Dar University, College of Medicine and Health Sciences, Bahir Dar, Ethiopia. Tel.: +251.920249001
E-mail: endalew02@gmail.com

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Abstract

Cutaneous leishmaniasis (CL) is caused by *Leishmania* parasites. Ethiopia is one of the top ten countries with a high CL load, and Amhara National Regional State (ANRS) is one of the CL hotspot areas in the country. This study examined cutaneous leishmaniasis's epidemiology and clinical profiles in the ANRS region. It was conducted from April to October 2023 across eight Leishmaniasis Treatment Centres (LTCs). A data review was done from patients presenting to these centers between June 2018 and July 2023. Chi-square test and logistic regression were performed using SPSS-23. A total of 1729 patients with CL were recorded, resulting in an overall burden of 8.6 cases per 10,000 outpatients. Patients were from 112 districts, and most of them (71.1%) presented with localized cutaneous leishmaniasis (LCL). Approximately 12% of patients lived with the disease for over a year without treatment, while 13.2% of patients were multiple-time comers. Cutaneous leishmaniasis continues to be a significant public health issue in the ANRS region. Approximately one-third of CL patients exhibit the mucocutaneous leishmaniasis (MCL) clinical form. There has been a notable delay among CL patients in seeking diagnosis and treatment. It is essential to conduct large-scale community-based studies and studies focused on both traditional and modern treatment centers to accurately estimate the prevalence of CL in the region. Follow-up and molecular studies are crucial for enhancing our understanding of the clinical features of the disease. Furthermore, raising community awareness about CL prevention and control can help patients obtain early diagnosis and treatment.

Introduction

Cutaneous leishmaniasis (CL) is one of the major public health problems worldwide, especially in low- and middle-income countries.[1] Cutaneous leishmaniasis is more prevalent than fatal visceral leishmaniasis (VL), affecting over one billion people in endemic areas globally, with an estimated more than one million new cases of CL occurring each year.[2-4] The CL is caused by *Leishmania* parasites and spread by the bite of a phlebotomine sand fly. Leishmaniasis (both CL and VL) is the second cause of death attributed to vector-borne parasitic disease next to malaria.[5] It is mainly presented in three different clinical forms:[6,7] localized CL (LCL), mucocutaneous leishmaniasis (MCL), and diffused CL (DCL). LCL is usually self-healing over time, while the latter two are non-healing forms causing deformity of affected areas and are associated with high social stigma.[8,9]

Ethiopia is one of the East African countries that faces a sig-

nificant burden of cutaneous leishmaniasis.[10-12] There are 30 million people at risk.[13-15] The CL has been known in the country since 1913 in Kutaber,[10] one of the CL endemic sites. However, CL is one of the country's neglected tropical diseases (NTDs). Our recent work in the Lay Gayint district, Northwest Ethiopia, showed that significant proportions of the CL cases have low knowledge about the disease and use traditional drugs (Yizengaw 2024, unpublished data). Ethiopia shows low awareness and knowledge of the community regarding CL.[4,10,11,16,17]

Currently, in ANRS, it is spreading and covering new areas that were previously not endemic to CL.[12] Different environmental factors such as changes in temperature, expansion of irrigation, deforestation, climate changes, and development of drug resistance[12,17] could be the factors for the spreading of CL. Local war, poor socioeconomic status, and poor access to health facilities that can diagnose and treat CL are also major contributors to the spread of this disease.[12]

According to the Amhara Regional Health Bureau (ARHB) 2018 report, the common CL endemic sites include Gayint, Addis Zemen, Finote Selam, Ankesha, Boru Meda, Sekota, and Kutaber. However, there is a scarcity of research dealing with CL's overall burden and clinical characteristics in ANRS. This study aimed to determine the epidemiology and clinical profiles of CL in eight leishmaniasis treatment centers in ANRS.

Materials and Methods

Study area

This multicenter retrospective study was conducted from April to October 2023 at Leishmaniasis Treatment Centres (LTCs) of: Addis Zemen Hospital, located in South Gondar Zone; Addis Alem Hospital, a primary hospital in Bahir Dar City; Fenote Selam Hospital, in West Gojjam Zone; Agewgemjabet Hospital, in Awi Zone; the University of Gondar Hospital, in Central Gondar Zone; Boru Meda Hospital, in South Wollo Zone; Nefas Mewcha Hospital, in South Gondar Zone; and Tefera Hailu Hospital, in Wag Hemra Zone (Figure 1).

The LTCs are established at different times. Thus, the data incorporated in this study from each center included different periods. Data were collected from CL patients registered in Addis Zemen Hospital LTC from June 2018 to August 2022, Addis Alem Hospital LTC from June 2018 to August 2022, Fenote Selam Hospital LTC from July 2018 to June 2022, Agewgemjabet Hospital LTC from August 2021 to July 2022, University of Gondar Hospital LTC from January 2022 to July 2023, Boru Meda Hospital LTC from October 2021 to February 2023, Nefas Mewcha Hospital LTC from January to March 2023, and Tefera Hailu Hospital LTC from August 2018 to April 2022.

The ANRS has a population of 22.5 million, according to the ANRS Plan Commission. The majority (79.9%) of the population live in rural areas, while 20.1% are urban dwellers. The healthcare system in the region consists of 100 government hospitals and 900 health centers. According to the ANRS Plan Commission 2019/20 report (unpublished), the altitude distribution of the region was as follows: between 500 and 1500 (29.3%), 1500 and 2300 (43.5%), 2300 and 3200 (24.2%), and >3200 (3.1%) meters above sea level.

Data collection

We retrieved the records of CL patients from each LTC, resulting in a total of: 492 CL patients from Boru Meda Hospital, 354

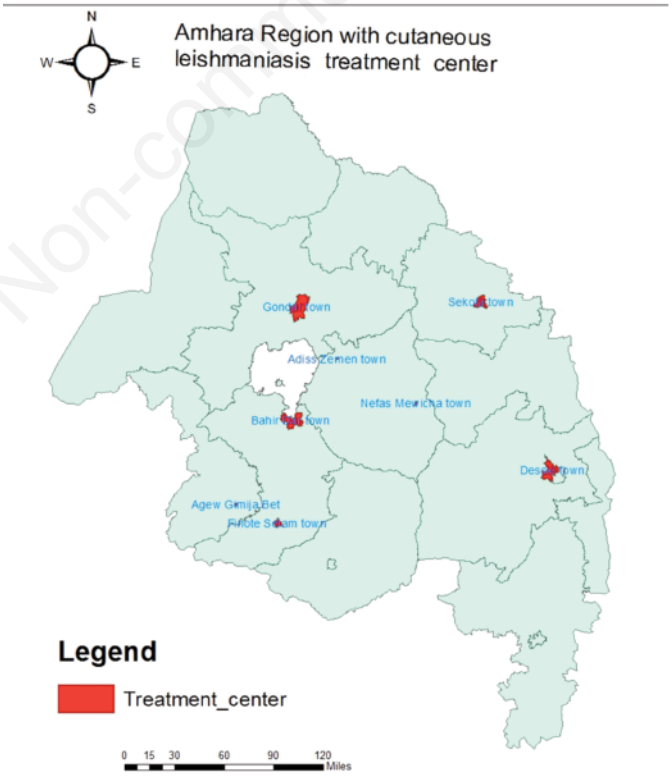

Figure 1. Leishmaniasis Treatment Centres in Amhara Region, September 2023 (Google Maps).

from Addis Zemen Hospital, 347 from University of Gondar Hospital, 147 from Nefas Mewcha Hospital, 126 from Addis Alem Hospital, 116 from Tefera Hailu Hospital, 94 from Fenote Selam Hospital, 37 from Agewgemjabet Hospital, and other 16 cases were not identified by treatment center. The data was retrieved using a structured data collection questionnaire developed for this purpose. The data collection questionnaire was comprised of: age, sex, CL type, treatment history, lesion size, duration of illness, microscopy result, and parasite load. Moreover, the total outpatient cases were retrieved from the triage registration logbook in each hospital. Inconsistent or incomplete patient data were excluded from the study. Patients were diagnosed and treated based on the Guidelines for Diagnosis, Treatment, and Prevention of Leishmaniasis in Ethiopia.[15] Patients' diagnoses were made using both parasitological parasite detection and clinical decisions. The parasitological diagnosis was made by parasite identification and quantification of the load from a skin slit smear under a microscope. A clinical decision was made by characterizing the skin lesion.

Inclusion and exclusion criteria

In the context of this study, all CL-confirmed patient records were included in each LTC since the establishment of the respective center. However, patient records with data previously published were excluded from the study.

Data quality management

Patient records with incomplete or ambiguous information in the registration logbook were meticulously cross-referenced with corresponding patient charts for further clarification. Health professionals working in the LTC of each hospital were consulted for unreadable information in the registration logbook. The completeness and consistency of the data were checked before analysis of the data.

Diagnosis and treatment of cutaneous leishmaniasis

The diagnosis and treatment of CL in the study hospitals were made based on the Guidelines for Diagnosis, Treatment, and Prevention of Leishmaniasis in Ethiopia.[15] Diagnosis of CL was based on parasitological detection of the parasite from a skin scraping smear and on clinical decisions. A skin scraping was taken from the active lesion and examined under a light microscope to detect and quantify the parasitic load of amastigotes. A clinical decision was made by characterizing the skin lesion.

Parasite load was determined for microscopy-positive CL cases. The parasite load was reported as follows: parasite load 6+=100 parasites per field, 5+=10–100 parasites per field, 4+=1–10 parasites per field, 3+=1–10 parasites per 10 fields, 2+=1–10 parasites per 100 fields, 1+=1–10 parasites per 1000 fields.

Confirmed CL patients were commonly treated with an intramuscular injection of sodium stibogluconate (SSG) 20 mg/kg/day for 28 days.

Data analysis

The data were entered and analyzed using Statistical Package for Social Science 23 (SPSS-23). The prevalence of CL was expressed per 10,000 total outpatient cases. The total outpatient cases were also retrieved from each study hospital during the same period. The percentage of different clinical forms of CL was calculated from the total CL cases. Both univariate and multivariate logistic regressions were used to measure the strength of the association. Variables with $p<0.25$ in the univariate analysis were entered into multivariate logistic regression analysis. A chi-square test was employed to assess the relationship between dependent and independent variables. Statistical significance was declared at $p<0.05$.

Results

Demographic variables

Of the total 2,019,217 outpatients, 1729 CL cases were diagnosed and treated in eight LTCs in the region. Of 1729 CL cases, 585 (33.8%) were females. The mean age of CL patients was 25.88±17.5 years. The highest numbers of CL patients presenting at the LTCs were in the 15-29 (44.7%) and <15 (25.6%) age groups. The age was not recorded for one patient.

Prevalence of cutaneous leishmaniasis

Boru Meda Hospital had the highest number of reported CL cases (492 cases). The pooled average prevalence of CL was 8.6 per 10,000 total outpatients registered in each hospital during the same period (Table 1).

Clinical characteristics of cutaneous leishmaniasis patients

The proportions of LCL, MCL, and DCL clinical forms were 71.1%, 28.1%, and 0.8%, respectively. A significant difference was seen in the distribution of CL clinical forms (χ^2:1296; $p<0.001$). Seven patients did not have clinical data recorded. Most CL patients were diagnosed and treated late, after six months of having the disease. The longest period without treatment for CL patients was 158 months, with a mean duration of 11 months (SD: 14.1 months). The median duration of illness was 7.5 months.

A total of 228 (13.2%) CL patients had previous treatment history and were considered multiple-time comers. Out of these repeat comers, 155 (68%), 65 (28.5%), and 8 (3.5%) had LCL, MCL, and DCL clinical forms, respectively (Table 2).

Table 1. Prevalence of CL among the total outpatients in ANRS, 2023.

Hospitals with LTC	Distance from Bahir Dar (Km)	Total outpatients	CL cases	Prevalence (per 10,000 outpatients)
Addis Zemen Hospital	88	235,941	354	15.0
Addis Alem Hospital	10	510,142	126	2.4
Agewgemjabet Hospital	131	56,761	37	6.5
Boru Meda Hospital	490	100,373	492	49.0
Fenote Selam Hospital	172	403,933	94	2.3
Nefas Mewcha Hospital	180	53,492	147	27.5
University of Gondar Hospital	172	417,580	347	8.3
Tefera Hailu Hospital	436	240,995	116	4.8
Total		2,019,217	1729	8.6

Skin scraping microscopy and duration of illness

From the registration logbook, we found that 954 (83.9%) CL cases were microscopically positive for *Leishmania* parasites. The slide positivity rate was higher in patients with a short duration of illness than those with a long duration.

Regarding the parasite density, only 208 slides were graded for parasitic load. Among these, the majority (54; 26%) were in grade two. The remaining 592 CL patients and microscopically negative CL patients (183) were diagnosed and treated clinically.

Lesion size of cutaneous leishmaniasis and associated factors

Duration of illness was found to be an independent explanatory risk factor for bigger lesion size. A multivariate logistic regression showed that duration of illness <6 months and 6-12 months showed a strong association (p=0.01 and 0.03, respectively) with lesion size (Table 3).

Discussion

This study describes CL's overall prevalence and clinical characteristics in ANRS, Northwest Ethiopia. Unlike previous studies, we enrolled a large dataset collected from all LTCs in the region. It showed that the overall prevalence of CL was 8.6 per 10,000 outpatients. This, however, does not represent the true burden of the disease, as there is underreporting of patients and a limited number of diagnosis and treatment centers for CL. A significant proportion of CL patients used traditional treatment in Ethiopia.[12,18] A similar study conducted at ALERT Hospital in Addis Ababa reported that 33% of outpatients were diagnosed and confirmed to have CL.[19] This higher prevalence might be because ALERT Hospital is well-known for treating skin diseases and serves as a referral center for CLs from all over the country.

The prevalence of CL per 10,000 total outpatient cases was higher in Boru Meda Hospital (49.0), followed by Nefas Mewcha

Table 2. Clinical characteristics of CL patients in ANRS, 2023.

Variable	Frequency	Percent	X^2 (p-value)
CL types			1296.5 (p<0.001)
LCL	1224	71.1	
MCL	484	28.1	
DCL	14	0.8	
Treatment History			932.6 (p<0.001)
New	1494	86.8	
Multiple-time comer (228, 13.2%)			
LCL	155	68%	
MCL	65	28.55	
DCL	8	3.5%	
Lesion size (millimeter)			40.6 (p<0.001)
≥4	570	(60.4)	
<4	374	(39.6)	
Duration of illness (month)			674 (p<0.001)
<6	309	32.1	
6-12	540	56.1	
13-24	54	5.6	
>24	59	6.1	

DCL, diffuse cutaneous leishmaniasis; LCL, localized cutaneous leishmaniasis; MCL, mucocutaneous leishmaniasis.

Table 3. Lesion size and associated factors for CL in ANRS, 2023.

Variable	Lesion size (centimeter)		Univariate analysis			Multivariate Analysis		
	≥4	<4	COR	95% CI	P-value	AOR	95%CI	P-value
CL type								
LCL	380	311	1.6	0.48-5.48	0.42	NA	NA	NA
MCL	180	57	0.63	0.18-2.18	0.46	NA	NA	NA
DCL	8	4	1	1	1	NA	NA	NA
Parasite load								
1+-3+	89	33	0.58	0.3-1.0	0.09	NA	NA	NA
4+-6+	46	29	1	1	1	NA	NA	NA
Sex								
Female	154	116		1	1	NA	NA	NA
Male	416	258	1.21	0.91-1.6	0.18	NA	NA	NA
Treatment history								
New	526	364	2.9	1.44-5.86	0.01	0.6	0.29-1.4	0.27
Multiple	42	10	1	1	1	1	1	1
Duration of illness (month)								
<6	126	135	4.5	2.1-9.7	0.01	2.7	0.12-0.63	0.01
6-12	258	197	3.2	1.5-6.8	0.01	4.1	1.18-0.93	0.03
13-24	32	7	0.92	0.3-2.7	0.89	1.6	0.47-5.56	0.44
≥24	39	9	1	1	1	1	1	1

AOR, adjusted odds ratio; COR, crude odds ratio; NA, not applicable; DCL, diffuse cutaneous leishmaniasis; LCL, localized cutaneous leishmaniasis; MCL, mucocutaneous leishmaniasis.

Hospital (27.5). This might be because the awareness of the CL cases and the community in the catchment area of Boru Meda Hospital is better, as it is the oldest CL treatment center in the region. Our previous work in Nefas Mewcha Hospital showed that the treatment-seeking behavior of CL cases was improved by the awareness training we did.[11] The lowest prevalence of CL cases per 10,000 total outpatient cases (2.3) was in Fenote Selam Hospital. The number of CL cases decreased due to a new LTC, Agewgemjabet Hospital LTC, which is very close. Even though the LTC in the University of Gondar Hospital is among the oldest LTCs in the country, it is basically established for VL cases.

Our study showed that CL was predominantly affecting children and the youngest population. This is similar to the trend in Ethiopia, where CL is more common in children, with the highest prevalence occurring between 10 and 15 years of age.[20-22] This might be because children have immature immune responses as compared to adults.[23] An alternative explanation may be the development of immunity to CL with previous exposure in adults. Prospective data showed this to occur with *L. infantum* in Iran,[24] suggesting that protective anti-leishmanial vaccines are achievable.[25] It also showed that more males (66.2%) were diagnosed and treated for CL. This might be attributed to gender-based differences in activities and roles, which could potentially lead to increased exposure to sandfly bites. A similar finding has been reported from a retrospective study at the University of Gondar Hospital Leishmaniasis Research and Treatment Centre, Northwest Ethiopia,[21] and at Boru Meda Hospital.[26] However, in Silte Zone, Southern Ethiopia, the frequency of CL infection between males and females was nearly the same.[27] Another study conducted in Tigray, northern Ethiopia, indicated that the odds of CL occurrence were 2.1 times higher in males than females.[28]

The age group between 15 and 29 years old was the most affected. Similar to other studies in Ethiopia, it is evident that CL affects a population with a wide age range.[10] In our study, it was found that people between the ages of 1 and 72 years were infected. However, it was indicated that the most affected age group was between 16 and 45 years old, accounting for 63.4%,[28] and 70.2%[29] of the total cases in Ayder referral hospital, Northern Ethiopia, and Boru Meda Hospital, Northwest Ethiopia, respectively. The difference might be explained by the population pyramid of the ANRS.

Most CL patients presented with LCL forms. It is the most common form of CL worldwide and in Ethiopia.[12,13,30] We also observed a higher number of CL patients with MCL clinical forms than other World Old reports. We had reported similar findings from Lay Gayint district.[11] This finding may not be solely linked to *L. aethiopica*. Patients with mucocutaneous leishmaniasis (MCL) tend to seek diagnosis and treatment more actively because MCL can cause significant disfigurement of the mucosal tissues. Additionally, another possible explanation could be co-infection with the *Leishmania* RNA virus, which can lead to more severe forms of MCL.[31] In our study, a few CL patients presented with DCL, suggesting that DCL may be rare in ANRS. Similar findings have been reported in other studies.[11,26] However, more DCL (22.9%) has been reported from Northern Ethiopia.[28] Furthermore, the exchange of genomic materials between *L. aethiopica* and other *Leishmania* species like *L. tropica* and *L. major* could contribute.[20]

The majority (56.1%) of CL patients lived with the skin lesion for a significant time (6 to 12 months) without being diagnosed and treated. This finding is supported by a study conducted in Boru Meda Hospital.[29,32] In our study, the average time that patients lived with the lesions was nearly 11 months. Other previous studies reported 12.9 months of illness.[32] There is a significant delay in diagnosing and treating CL patients, which may affect disease progression and complicate case management. This could be attributed to the lack of awareness and low knowledge of the community regarding CL,[4,10,11,17,22,33,34] which will contribute to the continuous transmission of CL.

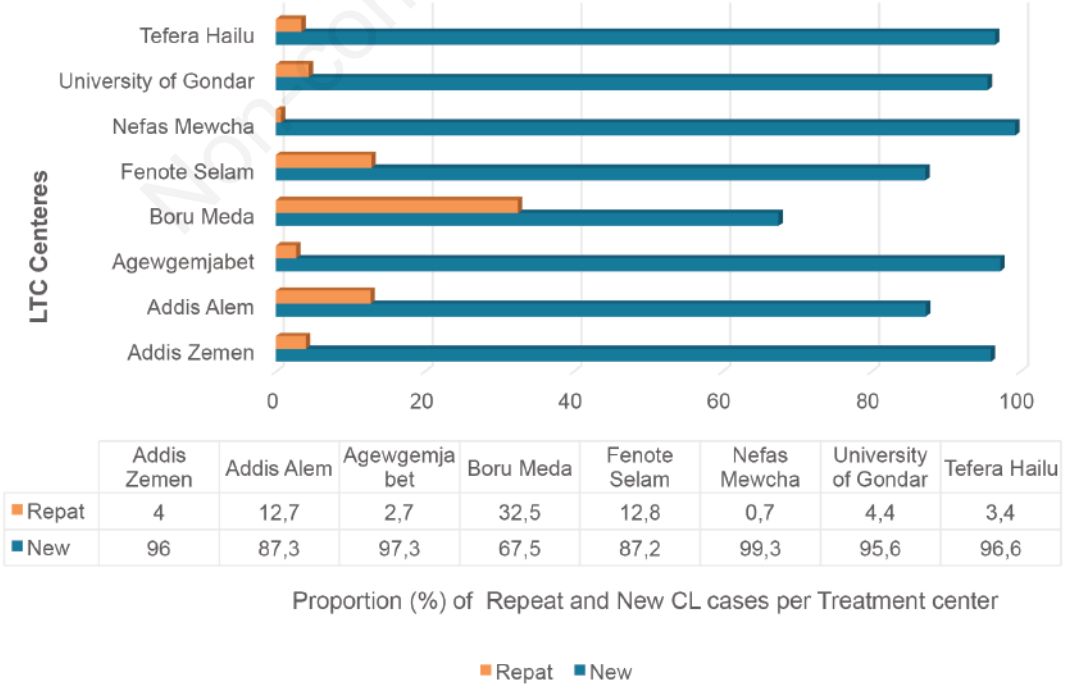

Figure 2. Proportions of both new and repeat (multiple-time comer) CL patients in ANRS, 2023.

Microscopic identification of the parasite was higher than previous reports by most studies.[19,22] This might be associated with the experience of laboratory technologists working in LTC. Health professionals and others working in hospitals with LTC are taking continuous training on CL, including its differential diagnosis. Skin slit smears from patients with MCL and DCL were more likely to test negative than those from LCL cases. About 21.5% of DCL and 21% of MCL patients had negative skin slit smear microscopic results. The number of LCL patients with negative smear results was only 13.9%. One possible explanation for this finding is that the MCL form of the disease primarily affects soft tissues, which makes it challenging to obtain an adequate sample for microscopic evaluation. Additionally, it is difficult to remove blood from the slit in soft tissues. Furthermore, the MCL form is associated with a lower parasitic load compared to the LCL and DCL cases. Moreover, DCL patients may experience superinfections due to delays in diagnosis. It makes sense, as most (57.1%) of DCL patients were multiple-time comers. Interestingly, our results also revealed an association between the duration of the disease and slide negativity. As the disease duration increased, the proportion of microscopically negative cases also increased linearly.

Our findings align with a study conducted at Boru Meda Hospital,[29] which reported a higher prevalence of CL in patients with lesions that are less than 12 months old compared to those with lesions older than 12 months. Similar findings were reported in a study conducted in Sri Lanka, where 54.5% of positive cases were found to have lesions for less than 6 months. There was a higher number of multiple-time comer DCL patients compared to those with other clinical forms. This might indicate a relatively lower response of DCL patients to the current treatment. Our finding agrees with existing previous research that indicated DCL cases pose a great challenge to treatment response, in which a potential treatment failure rate of 75% was recorded. Our study also noted that the highest number (32.5 %) of multiple-time comer CL patients was recorded at Boru Meda Hospital (Figure 2). It was not, however, possible to confirm the reason (*e.g.,* re-infection, treatment failure, or drug resistance associated with the parasite) for repeated visits of LTCs by CL cases in the region. A previous hospital-based study in Northcentral Ethiopia also reported that 367 (41.3%) patients were previously treated and returned to the treatment center.[17]

Conclusions

This study showed that CL is a major public health problem in Amhara National Regional State. According to our findings, one-third of CL patients presented with the MCL clinical form, and a relatively longer delay was observed among CL patients in seeking diagnosis and treatment. This delay in treatment not only increases the severity and burden of the disease on the population but also contributes to the ongoing transmission cycle of CL in the region.

Recommendations

Large-scale community-based studies in traditional and modern treatment centers should be included to estimate the number of CLs in the region**.** Follow-up and molecular studies are important to better understand the clinical features of the disease. Moreover, community awareness about CL prevention and control helps patients get early diagnosis and treatment.

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