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Original Article

Spatial Epidemiology of Clinical Forms of Cutaneous Leishmaniasis and Treatment Practice: Evidence from Leishmaniasis Research and Treatment Center, Northwest Ethiopia

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Abstract

Background: We aimed to conduct a comprehensive analysis of cutaneous leishmaniasis's (CL) clinical polymorphism by examining the relationship between clinical forms, duration of illness, and their spatiotemporal distribution.

Methods: A retrospective study at University of Gondar Hospital analyzed cutaneous leishmaniasis patients treated from 2022 to 2024. Demographic and epidemiologic data were collected, with parasite detection via microscopic and clinical examination.

Results: Overall, 454 CL cases from 49 districts were diagnosed, predominantly affecting males aged ≤30, with a mean age of 25.31 yr (SD ±18.3). Significant differences were noted in age and sex (P<0.05). Approximately 70% had lesions ≥4 cm. Most CL cases had 2+ parasite loads. Sodium stibogluconate (SSG) remained the primary treatment choice for patients. The spatial distribution of CL cases covered a larger geographical area, although the cases (>20) were concentrated in Central Gondar. The mucosal CL shared a similar geographical pattern with the recurrent CL type. Notably, 48% had chronic presentations and lived with the disease for ≥12 months. In diffuse CL (DCL) a longer delay was seen and its clinical presentation was associated with longitudinal time series. Acute patients exhibited a higher parasitic load than chronic ones (38% vs. 24%), respectively.

Conclusion: CL significantly affected school-aged children. The symmetrical distribution of cases in districts studied could increase the attention of clinicians and enhance management strategies. Extended disease durations necessitated specialized treatments for clinical transitions.

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Introduction

Vector-borne diseases account for 17% of global communicable diseases, risking 80% of the population and causing over 700,000 annual deaths (1). Cutaneous leishmaniasis affects 12 million people worldwide and disfigures human bodies and it is underreported in 67 countries by three to five times (2). The impact of the disease has surged, with DALYs from CL increasing by 43.5% between 1990 and 2016 (3). Previous study revealed insights into stigmatization of patients affected with CL (4).

Leishmania parasites need both sandflies and mammals to complete their life cycle, with over twenty human-pathogenic *Leishmania* species and thirty confirmed vector sandfly species (5). Phlebotomine sandflies are small insects measuring 2–3 mm in length that transmit parasites and spread disease (2). The incubation period for leishmaniasis varies by clinical form: cutaneous leishmaniasis typically lasts between 2 wk and 2 months, visceral leishmaniasis lasts between 3 and 9 months whereas mucocutaneous leishmaniasis can last up to 2 yr and beyond (6).

The balance of pro- and anti-inflammatory cytokines impacts disease presentation and outcomes, enabling *Leishmania* infections to alter based on immune response (3). Parasitic strain variations affect cutaneous diseases' lesions, spread, and treatment (7). Clinical presentation features patches, plaques, and nodules classified as localized, mucocutaneous, or diffuse types (7, 3). Diffuse cutaneous leishmaniasis, caused by *L. aethiopica*, leads to widespread skin lesions, particularly on the face, ears, and extremities (5).

Leishmania aethiopica accounts for over 99.9% of CL cases in Ethiopia (5, 8). *L. aethiopica* is common in highlands, while *L. major* and *L. tropica* predominate in lowlands (7, 5). In Ethiopia, *L. aethiopica* is transmitted by *Phlebotomus longipes* and *pedifer* while *L. tropica* and *major* are transmitted by *P. serenti* and *duboscqi* (7).

In sub-Saharan Africa, there is a lack of research concerning the epidemiology of CL (7). *L. aethiopica*, despite its significant impact, has been among the most overlooked species of *Leishmania*. Research is scarce on the prevalence of CL in Ethiopia, particularly in areas where *L. aethiopica* is endemic (8).

Few facility-based studies showed that the problem is prominent in the Amhara Regional State, one of the administrative areas in Ethiopia, and the prevalence is estimated to exceed 1.22% among outpatient attendants (9).

We aimed to analyze the clinical polymorphism of CL in relation to the disease's timeline. We hypothesized that CL can transition between clinical forms over time, with its characteristics also influenced by the duration of the illness. Understanding this dynamic is crucial for improving diagnosis and treatment strategies.

Materials and Methods

Study setting and area

The study was conducted at the Leishmaniasis Research and Treatment Center at the University of Gondar Hospital, City of Gondar. Patients from various regions sought treatment to this Hospital. It is located in northwestern Ethiopia at 12°03'N latitude and 37°28'E longitude, is approximately 727 km from Addis Ababa and 180 km from Bahir Dar, covering an area of 192.3 km² with a mountainous landscape (Fig. 1).

Fig. 1: Map of Gondar city administration, 2024

Study design and period

This cross-sectional retrospective study was conducted from Sep to Nov 2024 based on a two-year retrieved data from patients who were enrolled from Jul 2022 to Jun 2024.

Source population

All CL suspected patients who visited Gondar University Hospital in the study period.

Study population

CL-confirmed patients who had organized clinical and epidemiologic data

Diagnosis of cutaneous leishmaniasis

An experienced senior physician classified the clinical cases following Ethiopia's guidelines for diagnosing, treating, and preventing leishmaniasis (5).

The CL lesion was cleaned with 70% alcohol, scraped until tissue appeared, and the material was air-dried, fixed in methanol, stained with Giemsa 1:20 dilution for 20 min, washed, and examined microscopically with a 100× lens (2).

Grading of slides

Parasite grading done according to (5). Amastigote density was graded as follows: 6+ (>100/field), 5+ (10-100/field), 4+ (1-10/field), 3+ (1-10/10 fields), 2+ (1-10/100 fields), 1+ (1-10/1000 fields), 0 (none).

Clinical diagnosis of CL

LCL, MCL and DCL; definition of these clinical forms was found in previous publication (5).

Treatment of cutaneous leishmaniasis

Various therapeutic interventions, including local and systemic treatments, influence cutaneous leishmaniasis efficacy based on infecting species, region, and patient immunity (2). Ministry of Health of Ethiopia offers different treatment options (5), these are:

- **Intra-Lesion Administration of SSG**: For a few large lesions (< 3), weekly intra-lesional SSG for four to 6 wk can be used
- **Paromomycin**: is administered by intramuscular injection in a single daily dose of 14–15mg (sulfate)/ kg for 20–30 d.
- **Pentavalent Antimony Compounds or Meglumine Antimoniate**: 20mg Sb/kg/day IM or IV for 4–8 wk.
- **Miltefosine**: treat CL; dosages vary by weight: 150mg for >45kg, 100mg for 30-44kg, allometric for <30kg (10).

Spatiotemporal analysis

ArcGis was used to indicate and map the clinical forms of CL spatially by using shape files of the districts where cases came from.

Operational definition

Low parasitic load: A parasitic load having a load categorized as from +1 to +3

High Parasitic load: A parasitic load having a load categorized as from +4 to +6

Chronicity: The duration between the onset of symptoms and the period when the patient lives with the problem (6), in one year time it may progress from one form of disease to another.

- Acute CL disease: *Patients* Who live with the lesion and came < 12 months
- Chronic CL disease: CL patients, with lesions that have been reported or presented in ≥ 12 months

Clinical polymorphism: The presence of different forms of CL, treatment condition, lesion size, and parasitic load

Data collection and statistical analysis

Patient data for CL were collected from registration book and analyzed in SPSS. Spatial mapping was done using ArcGIS. Both descriptive and advanced statistical techniques was applied. Fishers' exact test and univariate logistic regression used to test significance at $P<0.05$.

Sample size and Sampling technique

All CL cases, who were treated from Jul 2022 to Jun 2024, were purposively included.

Data quality control and analysis

Data were collected by a trained nurse working for leishmaniasis patient care and standard formats were used from WHO, cleaned, coded and entered to a software.

Inclusion and exclusion criteria

Inclusion considered CL cases documented in the treatment registry and all data elements filled while exclusion considered unclear cases.

Ethical considerations

The Amhara Public Health Institute granted ethical approval for this study (NoH/R/T/T/D/07/83), with a support letter (APHI 03/1691). All data collected were anonymized.

Results

Demographic, Epidemiologic, and the Pathology of CL

In a two-year study 454 CL patients aged 2 to 90 were included, the mean age was 25.31 yr and the median age was 18. Localized CL predominated (61%), with illness durations ranging from 1 to 300 months. Patients delayed seeking treatment for an average of 14.5 months, with nearly half (48%) experiencing illness for over a year (Table 1).

CL risk mapping and spatial distribution

At the University of Gondar Hospital, CL cases varied significantly by district. Most cases came from nearby areas, while fewer than five came from distant regions, including a border area nearly 1000 km away. Notably, in areas between central and north Gondar no case was reported (Fig. 2).

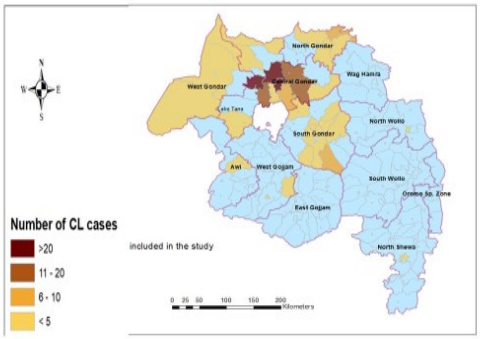

Fig. 2: Distribution of CL cases by district in Amhara Regional State, 2024

Table 1: Demographic and Clinical characteristics of CL, at University of Gondar Hospital, 2024

Variables		Frequency	%	Fisher's test (P-value)
Sex	F	159	35	
	M	295	65	0.001
	Total	454	100	
Age (year)	≤ 15	163	35.9	0.001
	16-30	169	37.2	
	31-45	43	9.5	
	46-60	53	11.7	
	>60	26	5.7	
	Total	454	100	
Districts, affected by CL	Gondar city	134	30.7	0.001
	Lay Armaciho	71	16.4	
	Chilga	30	6.8	
	Other woredas("districts")	185	42.4	
	Out of Amhara Region	16	3.7	
	Total	436	100	
	Number of districts	49		
CL forms	LCL	277	61%	0.001
	MCL	160	35	
	DCL	17	4	
Lesion size	<4cm	136	30	0.001
	≥4cm	315	70	
	Unclassified	3		
Chronicity/duration	<12month	229	52	0.418
	≥12month	211	48	
	Unclassified	14		
Parasitic load	1+	38	18.5	0.001
	2+	59	28.7	
	3+	38	18.5	
	4+	36	17.6	
	5+	22	10.8	
	6+	12	5.9	

The spatial distribution of LCL appears scattered, with a notable concentration of CL cases (over 20 cases) in certain districts. MCL and recurrent cases exhibit a symmetrical distribution in the spatial analysis (Figs. 2, 3).

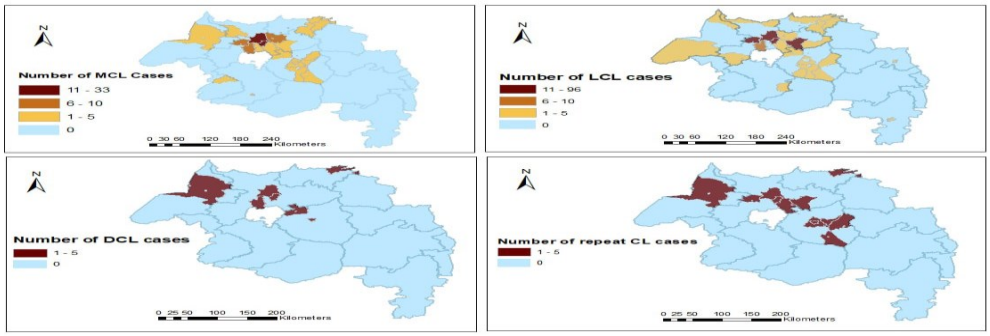

Fig. 3: Spatial distribution of different clinical forms of cutaneous leishmaniasis cases by district

Test of significance between CL forms and observed variables

More DCL cases were recurrent compared to other clinical forms. In each category of age LCL and MCL cases showed a similar pattern and distribution. SSG was the first choice of drug to treat all forms of CL. More DCL cases were chronic compared to other forms of the disease (Table 2).

Table 2: Cross tabulation for clinical, demographic and treatment status with CL forms

Variables		CL forms			Fisher's (*P*-value)
		LCL (%)	MCL (%)	DCL (%)	
Treatment Status	New	269(97.1)	139 (86.9)	11 (67.7)	0.000
	Recurrent	8 (2.9)	21 (13.1)	6 (35.3)	
	Total	277	160	17	
Treatment regimen	SSG	137(49.5)	90 (56.3)	6 (35.3)	NA
	PM	42 (15.2)	26 (16.3)	0 (0.0)	
	SSG+PM	0 (0.0)	3 (1.9)	2 (11.8)	
	Miltefosine	43 (15.5)	24 (15)	5(29.4)	
	Cryotherapy	23(8.3)	4(2.5)	0 (0.0)	
	Thermal	0 (0.0)	1 (0.6)	0 (0.0)	
	SSG+ Cryotherapy	5 (1.8)	0 (0.0)	0 (0.0)	
	PM+Miltefosine	1(0.4)	1 (0.6)	0 (0.0)	
	PM+ Cryotherapy	0 (0.0)	0 (0.0)	1 (1.9)	
	AmBisome	1 (0.4)	2 (1.3)	0 (0.0)	
	Unrecorded	25 (9)	9 (5.6)	3 (17.6)	
	Total	277	160	17	
Age (year)	1-15	99 (36)	57 (35.6)	7 (41)	0.92
	16-30	103 (37)	59 (37)	7 (41)	
	31-45	24 (8.6)	17 (11)	2 (12)	
	46-60	34 (12.2)	18 (11.2)	1 (6)	
	>60	17 (6.2)	9(5)	0 (0)	
	Total	277	160	17	
Sex	F	108 (40)	47 (29.3)	4 (23.5)	0.78
	M	169 (60)	113 (70.7)	13 (76.5)	
	Total	277	160	17	
Chronicity (delay)	<12 month	150(55.6)	74 (48)	5 (31)	0.008
	≥ 12 month	120(44.4)	80 (52)	11 (69)	
	Total	260	154	16	

SSG: Sodium stibogluconate, PM: Paromomycin

Test of correlation between observed variables with time series

The odds ratio (OR), a statistical model used to show the strength of association, in this case, the relationship between time elapse (chronicity) and with other of study variables found that the chronicity of CL was about two times higher in males than in females (*P*=0.009) and similarly, the DCL form of the cases (*P*=0.04) was strongly associated with chronicity of CL. The odds of the chronicity of the disease were 2.7 times higher in DCL patients compared to LCL patients. Bigger lesions are more likely to progress to chronicity than smaller ones (Table 3).

Table 3: Univariate logistic regression of chronicity of CL

Variables		Chronicity of CL disease		P-value	COR	95%CI
	Category	<12 month	≥12 month			
Sex	F	65(43.3)	85 (56.6)	1	----	----
	M	164 (57)	124 (43)	0.009	1.7	1.14----2.53
Age (yr)	1-15	84 (53)	74 (47)	0.9	0.95	0.4----2.2
	16-30	84 (51)	82 (49)	0.8	1	0.4----2.4
	31-45	27 (67.5)	13 (32.5)	0.2	0.5	0.1----1.4
	46-60	21 (40)	30 (60)	0.3	1.5	0.5----4
	>60	13 (52)	12 (48)	1	----	----
CL-type	LCL	150 (55.5)	120 (44.4)	1	----	----
	MCL	74 (48)	80 (52)	0.1	1.3	0.9----2
	DCL	5 (31)	11 (69)	0.04	2.7	0.9----8.1
Lesion size	<4cm	72 (54)	61(46)	1	----	----
	≥4cm	155 (51)	149 (49)	0.54	1.1	0.75----1.7

Parasitic load

Microscopic examination of *Leishmania* amastigotes parasitic load revealed no significant link with CL type, illness duration, or lesion size (P>0.05). Diffuse DCL had the highest parasitic load at 50%, with 34.5% of acute and 32% of chronic cases showing high counts [Data not shown].

Discussion

This study analyzed 454 cases from the University of Gondar Hospital to explore characteristics of cutaneous leishmaniasis and assess potential relationships among relevant variables.

More males (65%) were diagnosed and treated for CL disease compared to females and the occurrence of the disease between sexes showed that statistically significant (P=0.001). In line with our study, research showed more males, 59%, having CL lesions (11), likewise 67% of the cases (12), 56% of the cases in (13), and also in other studies males were highly affected by the disease (9, 14, 15). However, different reports have been shown in Saudi Arabia where the majority of CL cases were women and girls (4), while in Turkey, the ratio of males and females was very close (16). Data indicate that a higher disease burden in males is likely due to role differentiation, but methodology of the study and culture of the society might affect exposure equally.

Our research shows cutaneous leishmaniasis cases spanned ages 2 to 90, with a mean of 25.3 and a median of 18 yr, highlighting vulnerability in those ≤30. Nevertheless, further immunological studies are needed (8). In south Ethiopia, approximately half of the cases were children (57%) (17). Similarly, 50.9% CL cases were under 18 yr of age (16). Our previous data in Lay Gayint, showed that CL cases with the highest number (29; 38.7%) was in the age category of 16-30 yr (13), still cases of younger age group is more affected by the disease.

Elfaki and his colleagues reported a mean age of 28 ± 12.7 yr, ranging from 19 to 64 yr (4). A comparative study showed participants aged from two to 73 yr, with a mean age of 31.9, slightly higher than our findings (11). In a similar study area but in a different period, the study vivid that in Gondar, the median age was 23 yr (14), very close to the current finding. Complementing study also showed that young age groups were more affected, and (median age of cases was 21.5) (12). In anoth-

er related study, the median age of the participants was found to be 17 yr, and the mean was 22.1 (16). Other studies showed, individuals aged ≤ 20 yr were significantly impacted, with a mean age of 22.59 yr (9).

In our study, 48% of chronic CL cases had lesions over 12 months. The mean of illness duration was 14.5 months, median 9 months, versus 12 months in a similar study (14). In another study, the duration of illness varied from a month to 180 months (15). Most lesions of CL patients in south Ethiopia, were older than 6 months (77%) (17), although this study was a community-based study. A previous CL study showed a median lesion duration of 12 months (12). Another study analyzed the mean delay duration due to patient is 4.8 ± 2.6 months (16). A study revealed case delays of 2 to 20 wk, averaging 8.6 wk, with 93.2% unaware of treatment options and 3.4% knowing of insect transmission (4, 15). A qualitative study in Sri Lanka revealed that people often neglect seeking treatment for ordinary wounds and prefer staying home (18).

In our study, SSG was the primary treatment for CL, while another study found 30 d of IM SSG; 38.3% needed treatment adjustment (14), despite its limited effectiveness, SSG remains a primary treatment option alongside amphotericin B, paromomycin, and miltefosine (3). Due to treatment problems, in Boru Meda Hospital, Ethiopia, approximately one-third of the patients were recurrent (9). The effectiveness of treatment for American cutaneous leishmaniasis (ACL) varies with host factors; ulcerated lesions show a 25.8% failure rate, while early-stage ACL has a 75.0% failure rate, indicating that early treatment does not avert ulceration (19), further studies are needed to determine optimal treatment timing and lesion type for effective DCL management, as current cases show non-responsiveness (20). Another similar study indicated that disseminated leishmaniasis is a challenging disease to cure, presenting a high failure rate of 75% to pentavalent antimony therapy (21).

In our study, three forms of CL were observed: LCL (61%), MCL (35%), and DCL (4%). The chronicity of DCL was 2.7-fold higher compared to LCL (P<0.05). In other study, a potential transition from one clinical form to the other was reported (20), mucocutaneous leishmaniasis progressing to diffuse form. In endemic areas, the MCL type of the disease accounts 20% (6). A study in Gayint town, Ethiopia, classified the clinical types to LCL (68%), MCL (29.3%), and DCL (2.7%) (13). Likewise, a CL study in the same hospital like ours showed that, the clinical feature of CL and case number were dominated by LCL (8), then by DCL (7), and MCL (67) (14). All these findings were also substantiated by (15), in contrast to our report, 70.2% of CL patients had LCL, 20.8% had MCL, with few cases of DCL, recidivans CL, or mixed presentations were reported (15). Unlike our study, in a report (12), the most prevalent form of chronic CL was MCL at 50.0%, followed by DCL at 27.7% and LCL at 20.2%. In American CL, DCL incidence rose to 3.9%, with mucosal involvement noted in 53% of cases (21).

As a risk factor associated with the development of DCL in comparison to localized cutaneous leishmaniasis showed that: male sex, age under 19 yr (21), strain differences, treatment timing, and host responses might have contributed to observed variations. Researching these factors is essential for optimizing treatment duration and type (6).

Our research found significant parasitic loads 2+, ranging from 1+to 6+ (P=0.0001), while another study noted the highest cases at 1+, linking increased counts to disease progression (22). Our study found DCL had 1.9 times higher parasitic load; younger, new cases showed more parasites, while older, recurrent cases had lower loads (22). In Iran, a laboratory network enhanced cutaneous leishmaniasis diagnosis and surveillance, improving patient care through parasitological and molecular methods (23).

In this study, SSG was the primary treatment for CL, while miltefosine showed a 48.7% cure rate and 32.3% relapse (12). In a similar study, systemic pentavalent antimonial, as well as evidence from observational studies using systemic SSG indicates an efficacy of 19.2–89.5% (8). Treatment outcomes for SSG/allopurinol were poor; only 37 patients attended the second cycle, with 50% of the 36 who were followed were cured (24).

The clinical form of CL may vary due to host factors, duration, and parasitic nature. Spatial concentration of MCL cases could indicate local parasitic mutations and/or host factors. As previous spatial analyses are lacking, we recommend molecular and genomic testing to validate our epidemiological findings.

Our study lacked treatment outcome and molecular testing to determine if parasitic variation caused the uneven distribution of distinct clinical types of CL.

Conclusion

Our study highlights a high prevalence of CL among younger individuals, with larger lesions and significant treatment delays in DCL cases. Parasitic load variations require attention in management. The spatial distribution of cases suggests distinct epidemiological patterns, particularly for MCL and recurrent cases.

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Conflict of interest

All authors declared that there is no conflict of interest.

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