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# Frequency of Cutaneous Leishmaniasis and Complete Ulcer Healing in Patients Referred to Skin Diseases and Leishmaniasis Research Center, Isfahan, Iran from 2018 to 2019

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| ARTICLE INFO | ABSTRACT |
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| | **Introduction:** Iran is one of the most important hot spots for cutaneous leishmaniasis (CL) in the world. To date, no studies have been done on both epidemiological aspects along with the length of the treatment course of CL. This study aimed to determine the relative frequency of CL in patients with suspected skin lesions and the duration of healing after treatment with different regimens.<br><br>**Methods:** This cross-sectional study was conducted on patients with CL referred to the skin diseases and leishmaniasis research center (SDLRC) in Isfahan during the years 2018 to 2019. Among 389 patients with suspected skin lesions, 150 cases were included with proven CL. Information such as age, sex, education, location, size of the lesion, duration of treatment, and the rate of recovery were recorded. SPSS software version 20 was used for data analysis, the chi-square, Fisher´s Exact, and one Way ANOVA tests were used with a significant level of $p < 0.05$.<br><br>**Results:** Among 350 admitted cases, 150 cases were CL. positive (42.85%). The rate of complete recovery was higher in cases with an average age of 33.55 ±18.9 years, but these differences were not statistically significant ($P = 0.077$). There was 34 cases more than the other groups in this range of age. ( The rate of complete recovery in patients with a history of migration to endemic areas was higher than in patients without a history of migration ($P = 0.81$)). The rate of complete recovery in patients whose means treatment duration was $59.03 \pm 41.43$ days was higher than other recovery periods ($P = 0.23$).<br><br>**Conclusion:** The rate of complete recovery was higher in adult cases than the other groups. In this study, it was proved that the rate of recovery of patients had the significant relationship with the average duration of treatment.<br><br>**Keywords:** Cutaneous Leishmaniasis, frequency, Ulcer healing. |

## Introduction

Leishmaniasis is a worldly concern health problem and one of the parasitic diseases which have infected humans for many years. It is the most common disorder in tropical and subtropical regions of the world so that it is currently one of the first six diseases in these areas (1, 2). CL occurs in two forms: dry or urban and wet or rural by the parasites *L. tropica* and *L. major* respectively. The disease eventually heals with scarring and prolonged treatment (3, 4). The transmission of the parasite is mainly vectorial, through the bite of phlebotomine sand flies (5). It has been reported that more than 12 million people worldwide are struggling with leishmaniasis, and about two million new cases are added annually and CL is prevalent in more than 98 countries (6). According to the report published by the World Health Organization (WHO) in 2019, the annual incidence of leishmaniasis has been estimated to range from 700,000 to 1.2 million in the world (7). The disease is endemic in more than 70 countries, with 90% of cases occurring in Afghanistan, Algeria, Brazil, Pakistan, Peru, Saudi Arabia, and Syria. In the New World, it is found from the south of the United States to the north of Argentina. The annual incidence is estimated in 1-1.5 million cases (8). In Iran, about 20,000 new cases are reported each year, which is estimated that accurate statistics are about 4 to 5 times more than this number (9). The incidence of the disease in our country is approximately 28 per thousand people (10). The eastern Caspian Sea, southern and southeastern, and central regions of the country pose the highest rank of incidence. Involved factors in leishmaniasis include climate changes, environmental conditions, occupation, sex, and vegetation (11). Climate changes, including reduced rainfall, dam construction, river drying, deforestation, declining vegetation, agricultural expansion, and increased migration to cities and suburbs, cause the transition of the parasite and the leishmaniasis vector to disease-free areas so that it expands in these areas. Outdoor employment, such as animal husbandry, is another factor influencing exposure to the disease carriers and the incidence of the disease (12-16). Generally, the disease lasts for 6 to 18 months. Pentavalent antimony compounds are the first-line drug of treatment for leishmaniasis which are prescribed topically and systemically. Since the patient faced side effects including; Arrhythmia, increasing liver enzymes, anemia, thrombocytopenia, and leukopenia, and these drugs are not effective in cases of resistance to treatment (1, 6). Therefore, the implementation of operative measures to prevent the disease is necessary, which requires the diagnosis of at-risk groups and epidemiological factors associated with the disease in these areas. Due to the drying up some rivers and turning some agricultural lands into residential areas in Isfahan, the present study was conducted in 2018 to 2019 with the aim of an epidemiological survey of CL and the rate of ulcer healing in patients referred to the Skin Diseases and Leishmaniasis Research Center where is one of the main centers of leishmaniasis diagnosis and treatment in Isfahan, Iran, and its suburbs. This study aimed to determine the relative frequency of CL among patients with suspected skin lesions who admitted to the skin center and how long the various treatment regimens have led to recover. The demographic and epidemiological information about CL obtained in this study provides the latest available data. So far, no study has been conducted that, in addition to the epidemiological aspects of CL, considers the rate of healing and the duration of treatment in the city of Isfahan as one of the main hyperendemic centers of CL, and the present study has no similarity in this regard. Given that the epidemiological status of the disease may change over the years, it is necessary to repeat this type of epidemiological study a few years that is and leads to new understandings of the current situation.

## methods

This cross-sectional study was conducted on patients with CL referred to the skin diseases and leishmaniasis research center in Isfahan during the years 2018 to 2019. Each admitted case that their test was positive for CL included in the study. Out

of 389 patients, 150 had a positive leishmaniasis test. Patients enrolled in the study were not selective. Samples were taken from all patients referred to the laboratory for direct microscopic CL testing at the request of the physician. Inclusion criteria were as positive direct slide microscopy of CL with no history of CL treatment. The exclusion criteria were pregnancy, infants less than one-year-old or age more than 90 years old. Rest on this, the information of all patients who were referred to the center was recorded and included in the study. The sampling method was convenient. The tool of data collection was a questionnaire. Cutaneous leishmaniasis questionnaire is a standard questionnaire designed by the department of Health's research and technology based on the standards of CL. in endemic areas.

The questionnaire was completed by the head of the laboratory and the physician .The diagnosis was based on a direct microscopy skin sample test (3). Smears were taken from the margins of the suspected leishmanial ulcers using No. 15 Bistouries Blade Scalpel. For each patient, several smears were prepared and after drying at room temperature and fixed using methanol, they were washed after staining with Giemsa dye solution and examined for light microscopy to find out parasitic amastigote forms. Patients' necessary information such as age, sex, education, history of migration to endemic areas, history of the previous leishmaniasis, lesion size, lesion location, and the healing rate was collected and recorded in related checklists and statistically analyzed. According to the doctor's prescription, each patient was categorized into different treatment groups. Patients were followed up for 6 months. The decision about the healing of the lesion was based on the treatment protocol, which was considered a complete improvement if re-epithelialization of the lesion was observed. The size of the lesion includes its length and width. If the lesion size was diminished by 50 to 75%, it was considered as partial improvement, and no change in the lesion size, no improvement. Patient satisfaction, the induration size of the lesion, and morphology are

effective in determining the extent of lesion recovery (17). The publication of patients' information was done following ethical principles and the study was approved by the ethics committee of the Islamic Azad University, Science and Research Branch of Tehran, with code IR.IAU.SRB.REC.1398.085. In the case of children's participation, the consent form was signed by their parents. Although no intervention was made in the process of diagnosis and treatment of patients, patients were informed that their treatment process is followed and the extent of recovery and the duration of their treatment is evaluated. The principle of confidentiality of patients' information was observed and they were used only to achieve the objectives of the study.

The chi-square, Fisher´s Exact Test, and One Way ANOVA test was used for data analysis. The collected data were analyzed by using SPSS version 25 software. The significance level was set at 0.05.

### Results

The information of 150 patients with leishmaniasis who were referred to the Skin Diseases and Leishmaniasis Research Center from 2018 to 2019 was recorded in the relevant document. According to table 1, most of the people in the study were men (91 (60.7%)) (3). The mean age of infected people was $32.81\_+19.14$ and the highest age was 31 to 40 years. The minimum and maximum age of infection were 1 year and 83 years, respectively.

Table 1 shows the width of the lesion in most patients (26.7%) was 2 cm and in only one patient (0.7%) was 4.5 cm. In terms of mean lesion length, most patients were 3 cm (22.7%) 34 cm, one patient was 4.5 (0.7%) and another patient (0.5%) was 5.5 cm. The size of the lesion includes its length and width. The maximum and minimum width of the size of lesion were 6 and 0.5 cm, respectively. The maximum and minimum length of the lesion was 7 and 0.5 cm. Most people had a history of traveling to high-risk areas, but they had no history of ulcers based on the previous disease. Clinical characteristics showed that in most cases,

the lesions were on the hand and the least cases were on the patient's neck. Also, the mean length of the lesion on the patients' body was 2.37 ± 1.25. Most patients had a complete recovery. The maximum duration of treatment was 210 days (in 2 patients) and the minimum duration of treatment was 7 days (in 1 patient). The duration of treatment in most patients was 30 days (Table 1).

**Table 1.** Demographic and clinical characteristics of studied CL patients in 2018-2019.

| variables | | N ( % ) |
|---|---|---|
| Gender | Male | 91 ( 60.7 ) |
| | Female | 59 ( 39.3 ) |
| Age groups ( year) | 1-10 | 25 (16.7) |
| | 11-20 | 18 (12) |
| | 21-30 | 27 (18) |
| | 31-40 | 29 (19.3) |
| | 41-50 | 18 (12) |
| | 51-60 | 22 (14.7) |
| | 61-70 | 7 (4.7) |
| | 71-80 | 3 (2) |
| | 81-90 | 1 (7) |
| Education | Illiterate | 46 (30.7) |
| | Below diploma | 45 (30) |
| | High School Diploma | 48 (32) |
| | College education | 11 ( 7.3) |
| Body organ | arm | 67 ( 44.7) |
| | leg | 53 (35.3) |
| | face | 20 (13.3) |
| | neck | 1 (0.7) |
| | trunk | 9 (6) |
| Endemic emigration | Yes | 120 (80) |
| | No | 30 (20) |
| History of previous CL. | Yes | 6 (4) |
| | No | 144 (96) |
| CL. percent recovery | Complete recovery | 92 ( 61.3) |
| | Relative recovery | 42 (28) |
| | no recovery | 16 (10.7) |
| *Leishmania* species | *L. major* | 144 (96) |
| | *L. tropica* | 6 (4) |
| Mean (±SD) Length of the lesion (cm) | | 2.37 ± 1.25 |
| Mean (±SD) Ordinate of the lesion (cm) | | 2.52 ± 1.27 |

Table 2 shows most of the patients who recovered completely were women aged 21 to 30 years with a diploma. There was no statistically significant difference ($p = 0.51$) compared to the rest of the study group. In terms of clinical characteristics, most of the patients who recovered completely had a lesion on their hands and had no previous history of CL and they had a history of traveling to endemic areas that did not show a statistically significant difference ($p = 0.78$).

Variable were tested according to their distribution in two groups. In patients whose lesions completely healed, the history of the previous leishmaniasis was higher than in patients with partial or no improvement. But this difference was not statistically significant ($P = 0.81$). Most patients who had a complete recovery from the

lesion did not have a history of migration to endemic areas, but in patients who had a relative recovery (healing) and no improvement, most people had a history of migration to these areas. This difference was not statistically significant ($p$ = 0.78). More *L. major* was isolated from the ulcers of patients than *L. tropica* with complete healing. These differences were not statistically significant ($p$ = 0.48).

**Table 2.** Relationship between healing rate and demographic and clinical variables of patients in 2018-2019.

| Variables | | Recovery status | | | p |
|---|---|---|---|---|---|
| | | No (n=16) | Relative(n=42) | Complete(n=92) | |
| Mean of age (year) | | 29.94 ±19.3 | 32.26 ± 20 | 33.55 ±18.9 | 0.077* |
| Sex | Female | 3(18.8) | 19(45.2) | 37(40.2) | 0.18** |
| | Male | 13(81.3) | 23(54.8) | 55(59.8) | |
| Education | Illiterate | 7(43.8) | 10(23.8) | 29(31.5) | 0.69*** |
| | Elementary literacy | 4(25) | 16(38.1) | 25(27.2) | |
| | High school Diploma | 4(25) | 12(28.6) | 32(34.8) | |
| | College education | 1(6.3) | 4(9.5) | 6(6.5) | |
| Body organ | Arm | 9(56.3) | 20(47.6) | 38(41.3) | 0.91*** |
| | Leg | 4(25) | 13(31) | 36(39.1) | |
| | Face | 2(12.5) | 7(16.7) | 11(12) | |
| | Neck | 0(0) | 0(0) | 1(1.1) | |
| | Trunk | 1(6.3) | 2(4.8) | 6(6.5) | |
| Mean (±SD) Length of the lesion (cm) | | 2.59 ± 0.9 | 2.21 ± 1.16 | 2.41 ± 1.35 | 0.54* |
| Mean (±SD) Ordinate of the lesion (cm) | | 2.63 ± 1.07 | 2.43 ± 1.2 | 2.55 ± 1.34 | 0.83* |
| History of CL. | Yes | 1(6.3) | 2(4.8) | 3(3.3) | 0.56*** |
| | No | 15(93.8) | 40(95.2) | 89(96.7) | |
| Endemic emigration | Yes | 13(81.3) | 35(83.3) | 72(78.3) | 0.87*** |
| | No | 3(18.8) | 7(16.7) | 20(21.7) | |
| Mean (±SD) of follow up (day) | | 76.69 ± 7 | 60.4 ±38.6 | 59.03 ± 41.43 | 0.24* |
| *Leishmania* species | L. major | 16(100) | 41(97.6) | 87(94.6) | 0.83*** |
| | L. tropica | 0(0) | 1(2.4) | 5(5.4) | |

*based on One Way ANOVA test;     **based on Chi-square test ***based on Fisher´s Exact test

## Discussion

Scarring and unwanted pharmaceutical side effects in people with CL can cause unfavorable physical and psychological effects. Considering infection prevention and controlling the causing agents and vectors of the disease is the most effective way to deal with leishmaniasis. In the current study, the number of cases was higher in men than in women. In the study of Nilforouzadeh et al. in Isfahan, the incidence of the disease was higher in men (61.8%) than women (38.2%)(10). In studies conducted in Ilam, 64.1%, in Andimeshk 56%, in Khorasan Razavi 52%, in Khatam Yazd 61%, and Hamedan 93.8% of cases of the disease occurred in men, which is a statistically significant difference (6, 18-20), but in Lamerd city the number of cases was higher in women (51.8%) than men (48.1%) (21). In the study of Piroozi et al. from 1977 to 2015, the incidence of the disease was higher in males than females (19). Among the reasons for the higher incidence of the disease in men, we can mention their employment outdoors, less clothing and body cover, and exposure to the disease carriers.

The findings of the present study showed that most cases of the disease occurred in the age group of 31- 40 years and the mean age of infection was 32.81±19.14. In a study conducted in Isfahan by Nilforoushzadeh et al. from 2001 to 2011 and Nejati et al. in Andishmak in 2013, the highest incidence of the disease was in the age group of 10-30 and 15-24 years, respectively (10, 18). The

chances of developing CL increase with travel and migration to endemic areas. Also, travel and migration are more likely among active people in terms of age than other ages, so in the present study, most cases of involvement occurred in the age group of 40-31 years.

According to the findings of the present study, most lesions due to CL were on the hands and the least on the neck. In a study conducted by Nilforoushzadeh et al., Conducted in Isfahan from 2001 to 2011, the most common lesions were on the hands (32.3%) and feet (24.1%) (10). In Ilam, the highest location of the lesion was on the hands (52%) and the lowest on the trunk (3.6%) of the cases, which is a statistically significant difference (22). In Andimeshk, the most common site of the CL ulcer was the hands and then the feet (18). In Lamerd, the most and the least involved organs were hand and trunk (21). In Pakistan, the most involved organs were hands (23.7%) (20). Because the leishmaniasis vectors are not able to bite on clothing, they mainly bite areas of the body that are not covered. Therefore, more lesions are expected to be seen on the hands, feet, and face.

Due to the results of the present survey, the incidence of leishmaniasis was higher in patients who migrated to endemic areas during the past year than in patients who did not migrate. Also, traveling or migrating to endemic areas causes epidemiological changes. For example, the isolation of *L. major* from patients in Pakdasht city in Tehran has been due to travel to Sabzevar because this city is the main area for *L. major* (23). Migration to endemic areas of CL in spring and summer is one of the main causes of leishmaniasis in the coming months. For example, people who have a history of migrating to endemic areas of leishmaniasis such as Harand, Segzi, Varzaneh, Natanz, and Agha Ali Abbas, increase the risk of developing the disease. Therefore, in this study, the rate of leishmaniasis is higher among people who immigrated to endemic areas than people who have not immigrated.

In the present study, the rate of complete ulcer healing was greater than the relative healing and non-healing. During the study of A al-khavajah et al. as well as the study of Sadeghian et al., It was concluded that the recovery rate of leishmaniasis decreases because of the secondary bacterial infection (24, 25). Therefore, secondary bacterial infection can be one of the factors which affected the rate of disease recovery. So far, the first line of treatment for CL has been glucantime; However, the effectiveness of this drug is reduced due to secondary bacterial infections. Therefore, clinicians also prescribe antibiotic therapy if they observe a secondary bacterial infection with leishmaniasis lesions.

50% trichloroacetic acid solution (50% TCA) can be used topically in the case of glucantime is not available as the first-line treatment of CL. Nilforouzadeh et al. In 2014 found that the use of this solution accelerates recovery and reduces the recovery duration of leishmaniasis (26). In case of drug allergy to glucantime or failure of glucantime treatment, one of the alternative drugs is 50% TCA solution. According to previous studies, this solution has had positive results in the rate of recovery and the duration of treatment. Therefore, in the present study, this solution was used according to the treatment protocol.

At present, the smallest and largest lesions were 0.5 and 6 cm in diameter, respectively. According to the study of Mokhtari et al. during the years 1987 to 1992, the largest and smallest lesions were reported to be 8 and 0.5 cm, respectively, which is consistent with the present study (27). One of the most important factors influencing the size of the CL lesions is probably the level of the patient's immune system. Immunocompetent patients are more likely to limit the size of the lesion in the short term. Another possible factor affecting the size of the lesion is a regular follow-up of patients. On-time referral to medical centers helps to limit the size of the lesions.

During the surveys conducted in the present study, the highest incidence of CL was observed in people with diploma degrees (32%). During the study of Lotfi et al. In 2017, 41.3% of the patients had elementary education while 10% were illiterate (i.e., they were unable to read and write) (28). In the present study, among the reasons that caused

more leishmaniasis in cases with high school knowledge level, the following possible reasons can be considered: The level of awareness about this disease, so this group probably did not have enough information about transmission cycles. For example, not knowing the peak time of biting sandflies, which is spring and summer, and the incubation period of the disease, which is the time between sandflies bites to the onset of the disease or even the short length of sandflies' proboscis that is not able to transmit the infection from the covered region of the body and are more likely to infect open areas such as hands and faces.

Some of the limitations of this study were as follow: 1. constricted sampling area to the SDLRC in Isfahan, 2. patients live in cities around Isfahan and their referral to this center for diagnosis and treatment is a difficult issue, Lack of accurate information about the species in people who have been infected by traveling to other parts of the country, the unknown location of infection and the bite of mosquitoes.

Because conducting epidemiological studies on a large scale will increase the validity of the results and the present study was limited to the admitted cases to Dermatology and Leishmaniasis Research Center, Isfahan University of Medical Sciences, so it is suggested that the next study will be done in Isfahan and the suburbs that are considered endemic areas of the CL and even other endemic cities of the CL. Also, the relationship between demographic and clinical variables with the rate of improvement in other endemic areas should be investigated and compared with the present study to finally adopt effective policies such as spraying and rodent control and no construction in desert areas to control the spread of the disease. Also, information about leishmaniasis such as transmission through sandflies, time of sandfly bites, the incubation period of several weeks to several months, use of appropriate cover to protect against sandfly bites, information about the benefits of regular follow-up of patients by personnel of health cares of medical centers to complete the treatment process, can be increased the rate of complete recovery of patients.

## Conclusion

In the present study, the majority of patients with CL were men. The shortest and longest treatment periods were 7 and 210 days, respectively. The rate of complete recovery was higher in cases with an average age of 33 years than in other age groups. In this study, it was proved that the rate of recovery of patients had the significant relationship with the average duration of treatment.

## Acknowledgments

## Conflict of Interest

The authors declare that they have no conflict of interest in this study.

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